# Nintedanib attenuates lung function decline in a bleomycin-induced rat model of pulmonary fibrosis

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## Introduction

Pulmonary fibrosis is an interstitial lung disease characterised by scarring of the lung tissue leading to a decline in lung function which eventually becomes fatal. There are currently very limited treatment options and even with treatment the life expectancy after diagnosis is only three to five years.

Nintedanib is a small molecule tyrosine kinase inhibitor that has recently been clinically approved for the treatment of idiopathic pulmonary fibrosis, having been shown to slow down the decrease in forced vital capacity observed in patients of pulmonary fibrosis.

The aim of this study was to evaluate the effect of prophylactic and therapeutic nintedanib treatment on changes in inflammation, fibrotic biomarkers and specifically lung function in a preclinical rat model of bleomycin-induced pulmonary fibrosis.

## Methods

Male Sprague Dawley rats were administered bleomycin sulfate (3 IU/kg) or saline by intratracheal instillation on Day 0. Oral treatment with nintedanib (100 mg/kg q.d.) commenced prophylactically prior to bleomycin administration on Day 0 or therapeutically on Day 7 after challenge.

Invasive airway mechanics using the eSpira Forced Manoeuvres System (EMMS) and measures of airway and lung tissue resistance and compliance using a forced oscillation system were assessed on Day 7 and Day 21. Lung inflammation and fibrosis were assessed by analysing bronchoalveolar lavage (BAL) cell counts and BAL TGF-β levels. Lungs were removed from the animals and weighed; the right lungs were then snap frozen for analysis of lung tissue hydroxyproline levels, and the left lungs fixed in 10% neutral buffered formalin for histopathological examination. This included modified Ashcroft scoring on Massons trichrome stained sections.

## Results

Intratracheal administration of bleomycin resulted in a significant decline in lung function, including changes in forced expiratory volume in 100 msecs ($FEV_{100}$), forced expiratory volume (FVC), whole lung elastance and tissue elastance, at both Day 7 and Day 21 post bleomycin administration. The significant decline in FVC and $FEV_{100}$ induced by bleomycin administration was greater at Day 21 (51 and 23% respectively) than Day 7 (43 and 22% respectively) (Figure 1). On Day 7 these changes in lung function were not affected by nintedanib treatment; however, at Day 21 prophylactic and therapeutic intervention with nintedanib resulted in a significant improvement in lung function correlating with a reduction in the Ashcroft score (Figure 2).

Prophylactic nintedanib administration also reduced wet lung weight, TGF-β levels in the BAL and lung tissue hydroxyproline content (Figure 3).

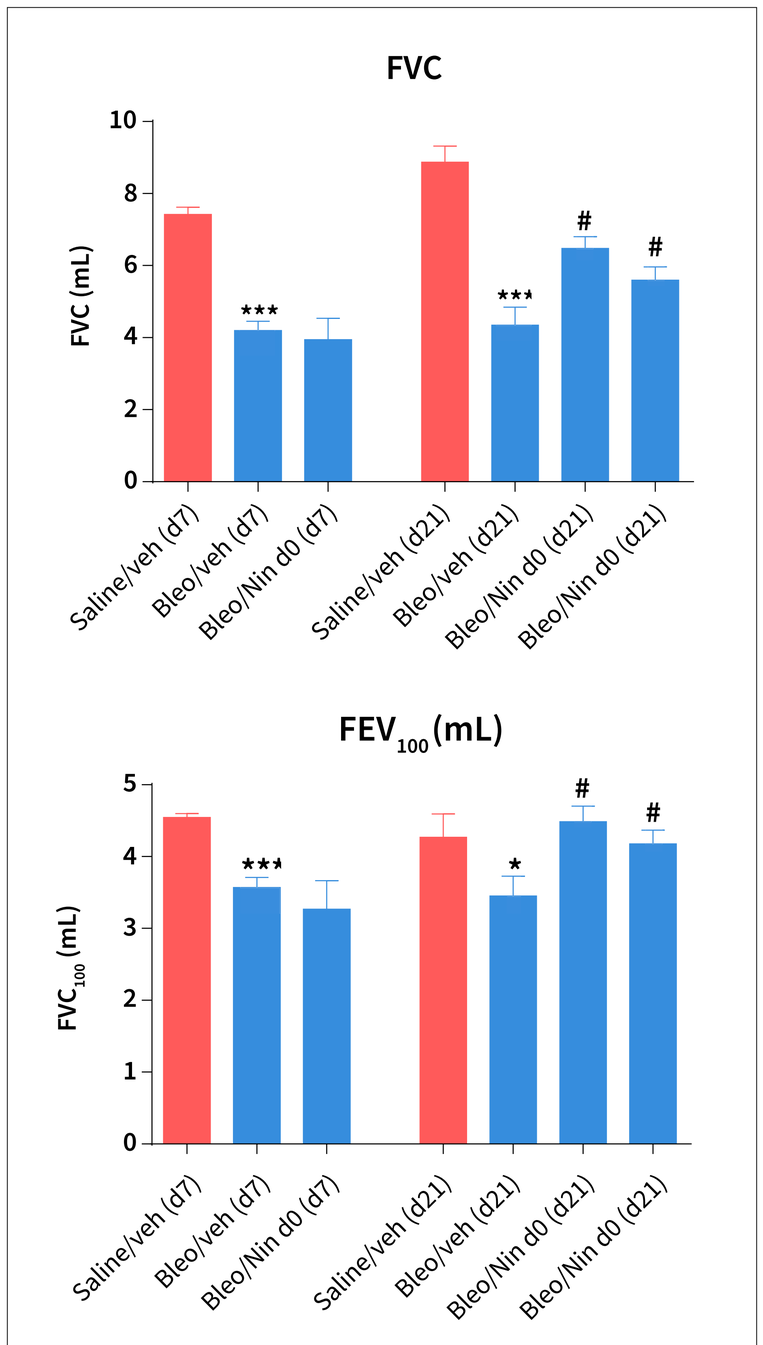


**Figure 1. Intratracheal administration of bleomycin** induces a significant decline in both FVC and FEV100 at Days 7 and 21 which is attenuated by both therapeutic and prophylactic nintedanib treatment at Day 21.

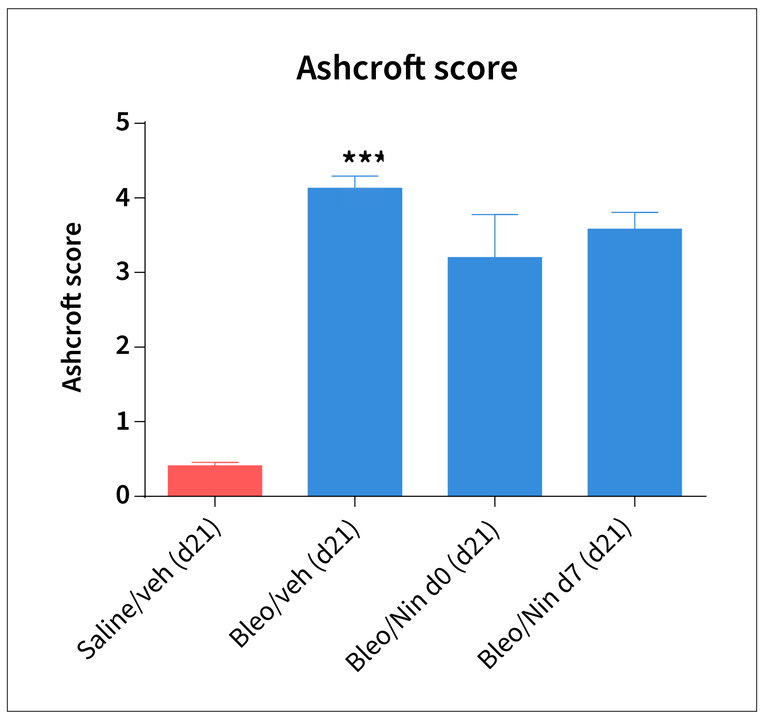


**Figure 2. Prophylactic and therapeutic nintedanib treatment** reduced the Ashcroft score on Day 21 correlating with an improvement in lung function.

*** p<0.001, p<0.01, * p<0.05 when compared to the saline/vehicle treated group, and p<0.001, ## p<0.01, # p<0.05 when compared to the bleo/vehicle treated group.

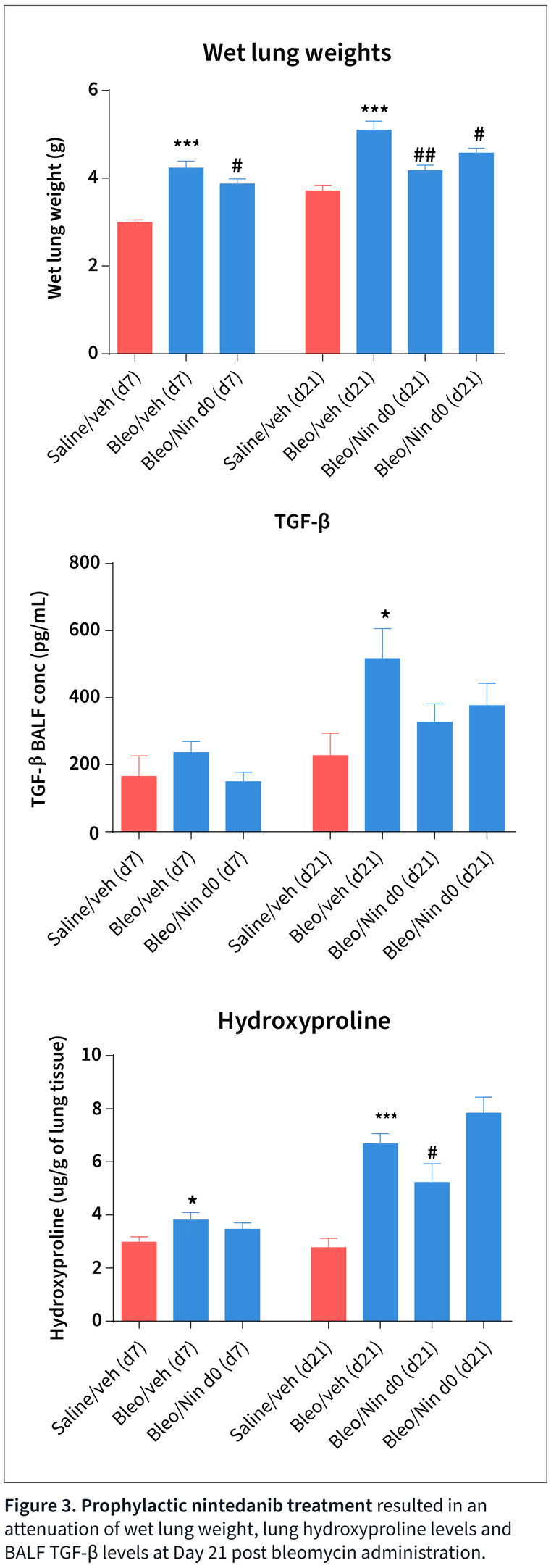


**Figure 3. Prophylactic nintedanib treatment** resulted in an attenuation of wet lung weight, lung hydroxyproline levels and BALF TGF-β levels at Day 21 post bleomycin administration.

## Conclusion

This model induces measurable changes in clinically relevant lung function endpoints and lung fibrosis biomarkers, which were attenuated by nintedanib treatment. More specifically, our findings suggest that inhibition of the fibrosis biomarkers of BAL TGF-β and tissue hydroxyproline by nintedanib translates to an attenuation of lung function decline at Day 21.

Animal experiments were conducted according to the Animals (Scientific Procedures) Act, 1986, and 2012 amendments following local ethical approval. Work was conducted in an AAALAC-accredited facility.

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