



## ARTICLE

Inhaled treprostinil and forced vital capacity in patients with interstitial lung disease and associated pulmonary hypertension: a post-hoc analysis of the INCREASE study.

## CLINICAL QUESTION

What is the effect of inhaled treprostinil on lung function in patients with fibrosing interstitial lung disease enrolled in the INCREASE study?

## SUMMARY

**Background:** INCREASE was a randomized, multicenter, placebo-controlled, phase 3 trial that evaluated inhaled treprostinil in patients with fibrosing ILD and pulmonary hypertension (PH). INCREASE met its primary endpoint of significant improvement in 6-minute walk distance (6MWD) with inhaled treprostinil. In the study, it was also noted that the patients randomized to inhaled treprostinil had improvements in FVC, which was collected as safety endpoint during the study. In this post-hoc analysis, the authors aim to characterize the effect of inhaled treprostinil on FVC in the overall study population and certain subgroups of patients according to baseline clinical characteristics.

**Methods:** Patients included in the INCREASE study were 18 years and older diagnosed with PH by right heart catheterization and with interstitial lung disease (ILD) based on chest CT imaging. Patients with connective tissue disease-related interstitial lung disease (CTD-ILD) were required to have an FVC < 70%. Patients were randomized to inhaled treprostinil or placebo in 1:1 fashion. No new antifibrotic therapy was allowed during the study duration. Pulmonary function testing (PFT) was a safety endpoint measured at baseline, week 8, and week 16 of randomization. The effect of inhaled treprostinil on PFT was evaluated in the entire population as well as the following subgroups: idiopathic interstitial pneumonia, including idiopathic pulmonary fibrosis (IPF), combined pulmonary fibrosis and emphysema (CPFE), and CTD-ILD. Effects on the acute exacerbation of the underlying disease, oxygenation, and hospitalization, among others, were also assessed.

**Results:** 326 patients were enrolled in the INCREASE trial. 146 patients had idiopathic interstitial pneumonia of which 92 (28% of the total population enrolled) had IPF. 82 (25%) had CPFE, and 72 had CTD-ILD. 49 (54%) of patients with IPF were on antifibrotic agents.

Inhaled treprostinil was associated with a non-significant increase in the placebo-corrected least squares mean FVC of 28.5 mL ( $p=0.35$ ) at week 8 and 44.4 mL ( $p=0.21$ ) at week 16. This corresponded to a statistically significant percent predicted difference in FVC of 1.8% ( $p=0.014$ ) at 8 weeks and 1.8% ( $p=0.028$ ) at 16 weeks. In subgroup analysis, patients with idiopathic interstitial



pneumonia showed a significant FVC difference at week 16 of 108.2 mL ( $p=0.023$ ), but not at week 8. Sub-analysis of the patients with IPF showed a significant difference in FVC favoring inhaled treprostinil at week 16 (168.5 mL,  $p=0.011$ ) and significant difference in percent predicted FVC at week 8 (2.5%,  $p=0.038$ ) and week 16 (3.5%,  $p=0.015$ ). Placebo-corrected response to inhaled treprostinil was more robust in patients with baseline PVR  $>5.275$  WU, and baseline NT-proBNP  $\geq 503.85$  pg/dL. The response was not affected by baseline FVC, DLCO % predicted, mean pulmonary artery pressure (mPAP), or 6MWD.

Patients on the anti-fibrotic agent nintedanib had a significant placebo-corrected difference in FVC (113.0 mL at 16 weeks,  $p=0.16$ ). When patients on anti-fibrotic agents were evaluated as a group those receiving inhaled treprostinil had no statistically significant difference in placebo-corrected FVC or percentage of predicted FVC. There was no difference in the most reported side effects, including cough, based on the disease subtype. Patients on inhaled treprostinil had significantly fewer events of acute exacerbation of the underlying lung disease.

**Discussion:** In the primary publication of the INCREASE study (Waxman A et al. NEJM 2021; 384: 325-334), treatment with inhaled treprostinil was associated with a statistically significant increase in FVC. Subgroup analysis in this study shows the effects are most pronounced in subjects with idiopathic interstitial pneumonia and IPF, suggesting treprostinil may have antifibrotic properties. NT-proBNP and PVR, markers of more severe pulmonary vascular involvement, were associated with greater improvements in FVC.

The study has limitations, including being a post-hoc analysis of an outcome that was collected as a safety endpoint, and thus is not powered to detect difference in FVC among disease subgroups. The outcome of acute exacerbation of the underlying disease was not centrally adjudicated and the number of events was higher in the study population than clinically expected.

## GROUP OPINION

As noted by the authors, the study has multiple limitations. FVC was a safety endpoint and INCREASE was not designed to test the effect of inhaled treprostinil on FVC. This post-hoc analysis is nevertheless important as the only two medications approved for IPF were approved based on their effects on FVC. The mechanism of treprostinil effect on FVC is not clear. Treprostinil has been shown to inhibit fibroblast growth and attenuate bleomycin-induced lung injury in mouse models. The relatively rapid effect seen in this analysis, at 8 weeks or 16 weeks, however, would suggest the outcomes may not be due to antifibrotic effects. Of note, the inhaled formulation was well-tolerated and may have resulted in decreased episodes of acute exacerbation of underlying lung disease. There is a larger, prospective study currently ongoing examining the effects of inhaled treprostinil in patients with IPF, independent from a PH diagnosis.



**Reference:**

Nathan, Steven D., et al. "Inhaled treprostinil and forced vital capacity in patients with interstitial lung disease and associated pulmonary hypertension: A post-hoc analysis of the INCREASE study." *The Lancet Respiratory Medicine* 9.11 (2021): 1266-1274.

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