

The Impact of Hemodynamic Parameters on Inhaled Treprostinil Treatment Response – A Subgroup Analysis from the INCREASE Trial



Aaron B. Waxman, MD, PhD¹; Victor Tapon, MD²; Reda E. Girgis, MD³; James R. Runo, MD⁴; Remzi Bag, MD⁵; Arunabh Talwar, MD⁶; Peter Smith, PharmD⁷; Dana Johnson, PhD⁷; Eric Shen, PharmD⁷; Steven D. Nathan, MD⁸

¹Brigham and Women's Hospital; ²Cedars Sinai; ³Michigan State University; ⁴University of Wisconsin; ⁵University of Chicago; ⁶Hofstra Northwell School of Medicine; ⁷United Therapeutics Corporation; ⁸Inova Fairfax Hospital

STUDY DESIGN

- INCREASE was a multicenter, randomized, double-blind, placebo-controlled, 16-week, parallel-group study of inhaled treprostinil in patients with pulmonary hypertension associated with interstitial lung disease (PH-ILD).
- Inclusion criteria included confirmed diagnosis of PH-ILD by right heart catheterization and demonstrated evidence of diffuse parenchymal lung disease on computed tomography imaging.
- The study met its primary endpoint of change in 6-minute walk distance (6MWD) and all secondary endpoints at Week 16.¹ Additionally, treatment with inhaled treprostinil was associated with significant improvements in forced vital capacity (FVC).²
- This post-hoc analysis evaluated the treatment effect of inhaled treprostinil on 6MWD and FVC as a function of baseline hemodynamics.

METHODS

- Mixed Models for Repeated Measures were used to analyze the impact of hemodynamic parameters (pulmonary vascular resistance [PVR], mean pulmonary artery pressure [mPAP]) on differences between treatment groups in 6MWD and FVC changes at week 16.
- Explanatory variables in the model were: treatment, visit, treatment x visit interaction, baseline 6MWD (or FVC), baseline hemodynamic parameter, and treatment x baseline hemodynamic parameter interaction.

RESULTS

- All patients with 6MWD or FVC values at baseline and at least one measurement post-baseline were included (n=302, 6MWD; n=287, FVC). Baseline PVR and mPAP values ranged from 3.06-18.05 Wood units (WU) and 25-74 mmHg, respectively, and were similar between treatment and placebo arms.

RESULTS: 6MWD

- For every additional 1 WU increase in baseline PVR, 6MWD treatment effect increased by 4.54 m in the inhaled treprostinil group compared to a decrease of 3.89 m in the placebo group (p<0.0001, Figure 1).
- For every additional 1 mmHg increase in baseline mPAP, 6MWD treatment effect increased by 0.32 m in the inhaled treprostinil group compared to a decrease of 1.18 m in the placebo group (p=0.0098, Figure 2).

Figure 1. Summary of Change from Baseline in 6MWD (m) at Week 16 Over Range of PVR Values

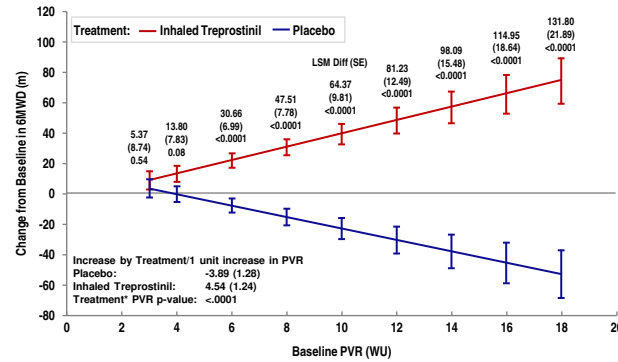
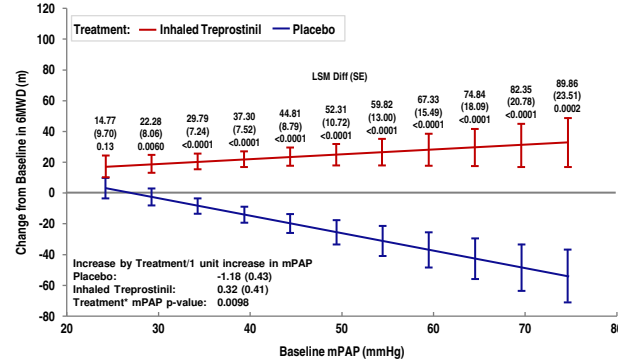


Figure 2. Summary of Change from Baseline in 6MWD (m) at Week 16 Over Range of mPAP Values



RESULTS: FVC

- For every additional 1 WU increase in PVR, FVC improved by 1.15 mL in the treatment group compared to -19.72 mL observed in the placebo group (p=0.0601, Figure 3).
- For every additional 1 mmHg increase in baseline mPAP, FVC improved by 0.21 mL in the treatment arm compared to -5.30 mL for those on placebo (p=0.1206, Figure 4).

Figure 3. Summary of Change from Baseline in FVC (mL) at Week 16 Over Range of PVR Values

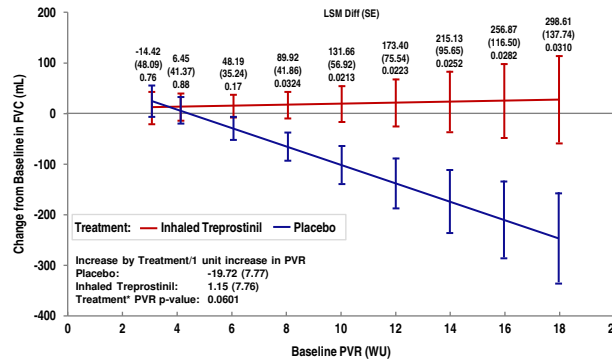
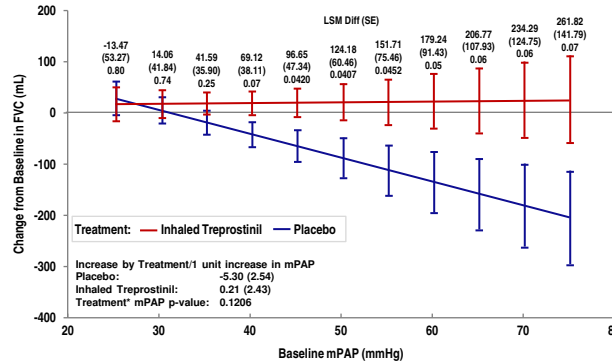


Figure 4. Summary of Change from Baseline in FVC (mL) at Week 16 Over Range of mPAP Values



DISCUSSION

- This analysis suggests a positive treatment effect of inhaled treprostinil on 6MWD in patients with PH-ILD when adjusted for baseline hemodynamic characteristics.
- Patients with PH-ILD that have more severe elevations in PVR derive greater improvements in exercise capacity likely reflecting improved right ventricular function associated with inhaled treprostinil.
- Similar improvements were observed with FVC that trended toward significance. These findings could reflect improvement in vasculature stiffness leading to less restriction in the lung parenchyma.

CLINICAL IMPLICATIONS

- Though the benefit of inhaled treprostinil in 6MWD was observed across the entire range of reported baseline values, patients with higher PVR and/or mPAP were more likely to have a more robust response to treatment.
- This analysis suggests higher PVR and mPAP reflect progressive pulmonary vascular remodeling and demonstrates the importance of considering pulmonary hemodynamics when treating patients with PH-ILD.

ACKNOWLEDGEMENTS

The authors would like to acknowledge all INCREASE sites, patients, and investigators for their participation in the study.

REFERENCES

- Waxman A, Restrepo-Jaramillo R, Thenappan T, et al. Inhaled Treprostinil in Pulmonary Hypertension Due to Interstitial Lung Disease. *N Engl J Med*. 2021 Jan 28;384(4):325–34.
- Nathan SD, Waxman A, Rajagopal S, 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. *Lancet Respir Med*. Published online June 29, 2021. DOI: [https://doi.org/10.1016/S2213-2600\(21\)00165-X](https://doi.org/10.1016/S2213-2600(21)00165-X).