The Impact of Inhaled Treprostinil on Patient Lung Function – Results from the INCREASE Study

Aaron Waxman, MD, PhD[1]; Ricardo Restrepo-Jaramillo, MD[2]; Thenappan Thenappan, MD[3]; Ashwin Ravichandran, MD[4]; Peter Smith, PharmD[5]; Lisa Edwards, PhD[5]; Victor Tapson, MD[6]; Steven D. Nathan, MD[7]

[1]Brigham and Women's Hospital; [2]University of South Florida; [3]University of Minnesota; [4]St. Vincent Medical Group, Inc.; [5]United Therapeutics Corporation; [6]Cedars Sinai; [7]Inova Fairfax Hospital

INCREASE

STUDY DESIGN

- INCREASE was a multicenter, randomized, double-blind, placebo-controlled, 16-week, parallel-group study.
- Inclusion criteria included confirmed diagnosis of pulmonary hypertension associated with interstitial lung disease (PH-ILD) by right heart catheterization and demonstrated evidence of diffuse parenchymal lung disease on computed tomography imaging.
- Patients receiving treatment for underlying lung disease were on a stable and optimized dose.

METHODS

- Pulmonary function testing (PFT) was conducted as a safety assessment at study Weeks 8 and 16. This current analysis provides further detail on inhaled treprostinil effects on the forced vital capacity (FVC) during the course of the study. FVC is the most widely accepted lung function measurement for the evaluation of fibrotic lung diseases.
- Exacerbation of underlying lung disease, defined as an acute, clinically significant, respiratory deterioration accompanied by evidence of new widespread alveolar abnormality, was assessed over the course of the study and by each Principal Investigator.

RESULTS

Baseline Characteristics

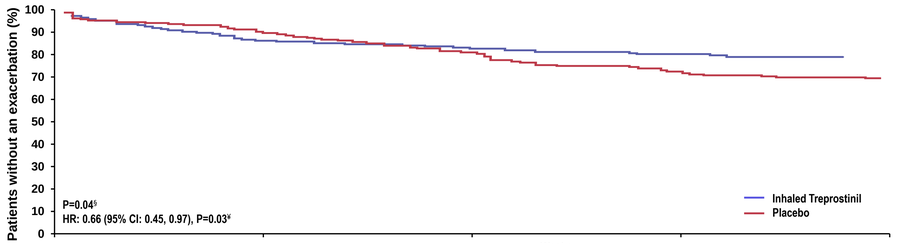
- A total of 326 patients were enrolled in the study.
- The most common PH-ILD etiologies included:
  - Idiopathic interstitial pneumonia (45%)
  - Idiopathic pulmonary fibrosis (28%)
- 14% of patients were on single background therapy with pirfenidone and 9% on nintedanib
- The median dose of inhaled treprostinil achieved at Week 8 and Week 16 were 10 and 12 breaths per session, respectively.

RESULTS

- Patients receiving inhaled treprostinil, compared to those receiving placebo, experienced significantly fewer exacerbations of underlying lung disease (43 [26.4%] versus 63 [38.7%]; p=0.02 by Fisher's exact test).

CI: confidence interval; HR: hazard ratio. Subjects who did not experience an exacerbation had their time to exacerbation censored at the study termination date. The confidence intervals have not been adjusted for multiplicity and cannot be used to infer definitive treatment effects.
§ P-value was calculated with log-rank test stratified by baseline 6-minute walk distance category.
¥ Hazard ratio, 95% CI, and P-value were calculated with proportional hazards model with treatment and baseline 6-minute walk distance (continuous) as explanatory variables.

Figure 1: Kaplan-Meier Plot of Time to Exacerbation of Underlying Lung Disease



# Pts at each timepoint	0	4	8	12	16
Inhaled Treprostinil	163	132	119	111	85
Placebo	163	138	117	96	70

- Overall, FVC improved with inhaled treprostinil by 28.47 mL and 44.40 mL at Weeks 8 and 16, respectively, when compared to placebo.
- Percent predicted FVC also improved at Weeks 8 (1.79%; p=0.0139) and 16 (1.80%; p=0.0277)
- Subgroup analysis of patients with etiology of idiopathic interstitial pneumonia (IIP) demonstrated FVC improvements of 46.48 mL and 108.18 mL (N=146, p=0.0229) at Weeks 8 and 16, respectively, and improvements in % predicted FVC at Weeks 8 (1.95%, p=0.0373) and 16 (2.88%; p=0.0096) compared to placebo.
- Further analysis for patients with etiology of idiopathic pulmonary fibrosis (IPF) demonstrated FVC improvements of 84.52 mL and 168.52 mL (N=92, p=0.0108) at Weeks 8 and 16, respectively, and improvements in % predicted FVC at Weeks 8 (2.54%; p=0.0380) and 16 (3.50%; p=0.0147) compared to placebo.

FVC: forced vital capacity; LS Mean: least squares mean; SE: standard error.
LS Mean (SE), P-values, estimated difference (SE), and associated 95% CIs are from the mixed model repeated measurement with the change from Baseline in FVC as the dependent variable; treatment, week, treatment by week interaction as the fixed effects; Baseline FVC as the covariate; and subject as the random effect. An unstructured variance/covariance structure shared across treatment groups was used to model the within-subject errors.

Figure 2a: LS mean change in FVC (mL) by week for overall ITT population

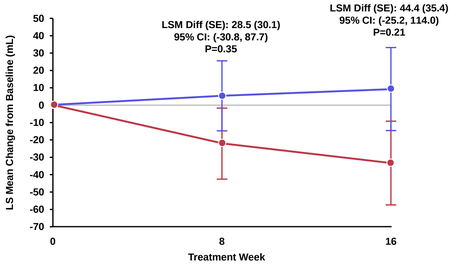
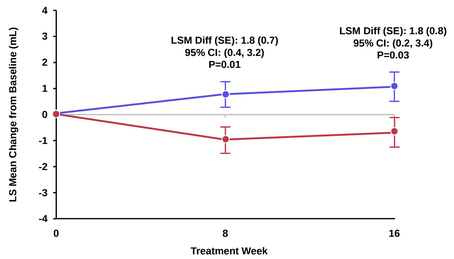


Figure 2b: LS mean change in FVC % predicted by week for overall ITT population



Treatment Group: Inhaled Treprostinil Placebo

Figure 3a: LS mean change in FVC (mL) by week for subset of patients with IPF

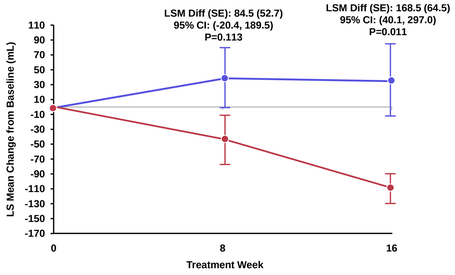
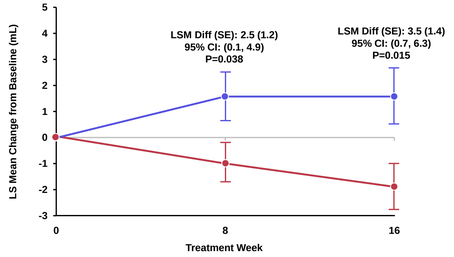


Figure 3b: LS mean change in FVC % predicted by week for subset of patients with IPF



DISCUSSION

- There was no deleterious effect of inhaled treprostinil on any PFT parameter during the study.
- Findings of a significant placebo-corrected difference in FVC combined with significantly fewer exacerbations in patients receiving inhaled treprostinil compared to those receiving placebo suggest that patients on inhaled treprostinil had a favorable impact on the course of the underlying lung disease. Along with preclinical evidence demonstrating the antifibrotic activity of treprostinil[1,2] this suggests that inhaled treprostinil may offer a treatment option for patients with ILD.
- Noted limitations of this analysis include the short duration of the FVC treatment follow-up of 16 weeks. Additionally, while there were fewer exacerbations of underlying lung disease in patients receiving inhaled treprostinil, the specifics of those exacerbations are unclear (e.g. disease progression vs. infectious exacerbations).

CONCLUSIONS

- The results of this study of inhaled treprostinil support an additional treatment avenue and might herald a shift in the clinical management of patients with ILD.
- Further consideration should be given to investigation of the safety and efficacy of inhaled treprostinil in patients with ILD in the absence of pulmonary hypertension.

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