Comparison of effects of inhaled treprostinil on lung function in patients with interstitial lung disease associated pulmonary hypertension and pulmonary arterial hypertension

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INCREASE

STUDY DESIGN

- The INCREASE study evaluated inhaled treprostinil (iTre) in a 16-week, randomized, controlled study in patients with pulmonary hypertension associated with interstitial lung disease (PH-ILD).
- The study met its primary endpoint of change in 6-minute walk distance (6MWD) at Week 16.[1]
- Improvement in forced vital capacity (FVC) was observed in patients randomized to iTre.[2]
- The aim of this post-hoc analysis is to compare lung function changes in the INCREASE study with the TRIUMPH study, which evaluated iTre over 12 weeks in patients with pulmonary arterial hypertension (PAH).

METHODS

- Pulmonary function testing (% predicted FVC and FEV1) was conducted at Baseline, Week 8, and Week 16 in the INCREASE study (n=326) and at Baseline and Week 12 in the TRIUMPH study (n=235). In both studies, PFTs were collected as a safety endpoint.
- Baseline characteristics, including age, gender, baseline 6MWD and baseline PFT, are compared by patients' group (TRIMPH versus INCREASE) using t-test or Wilcoxon test.
- For INCREASE, the mixed model repeated measurement (MMRM) was used to evaluate change in % predicted FVC and FEV1. In TRIUMPH, change in % predicted FVC and FEV1 was evaluated using ANCOVA; different statistical methods were used due to differing numbers of follow-up PFT values in each clinical trial. Analyses used observed data (no imputation performed).

RESULTS

- Baseline characteristics varied between patients in INCREASE and TRIUMPH (Table 1).

RESULTS

TRIUMPH

- No significant treatment difference for Week 12 FVC was observed in TRIUMPH (1.1%, SE 1.3%, p=0.40) (Figure 1a).
- There was no significant difference in % predicted FEV1 between groups at Week 12 (0.9%, SE 1.1%, p=0.37) (Figure 1b).

INCREASE

- There was a significant treatment effect with placebo-corrected improvements in % predicted FVC at Week 8 (1.8%; SE 0.7%, p=0.0139) and Week 16 (1.8%; SE 0.8%, p=0.0277) (Figure 2a).
- There was no significant difference in % predicted FEV1 at Week 8 or 16 between groups (Figure 2b).

Table 1: Baseline Characteristics

Baseline Characteristics	TRIUMPH (n=235)	INCREASE (n=326)	p-value
Age, mean (SD)	67 (12)	54 (13)	<0.001
Sex, n (%) Male Female	 44 (19%) 191 (81%)	 173 (53%) 153 (47%)	<0.001
Body mass index, kg/m^2 (median)	27.7	28.5	0.197
6-minute walk distance, (median)	359 m	259 m	<0.001
NT-proBNP, pg/mL (median)	624	504	0.795
Pulmonary function tests (median) FEV1, % predicted FVC, % predicted	 76% 82%	 63% 60%	 <0.001 <0.001

Figure 1: Change in lung function by visit: % predicted FVC

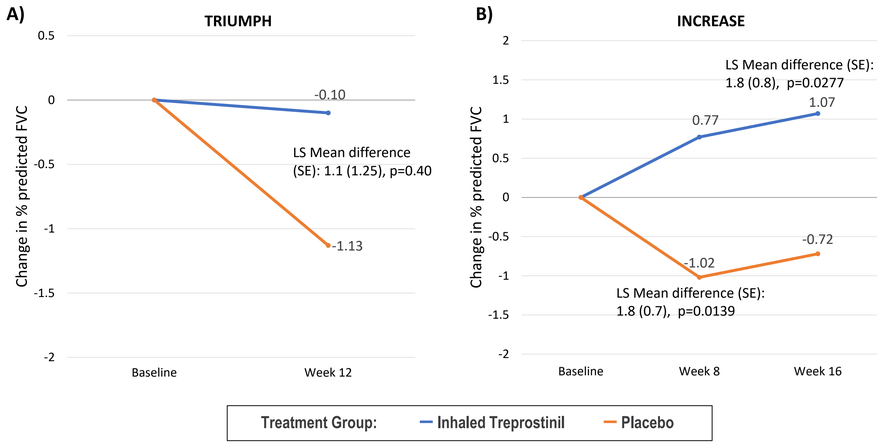
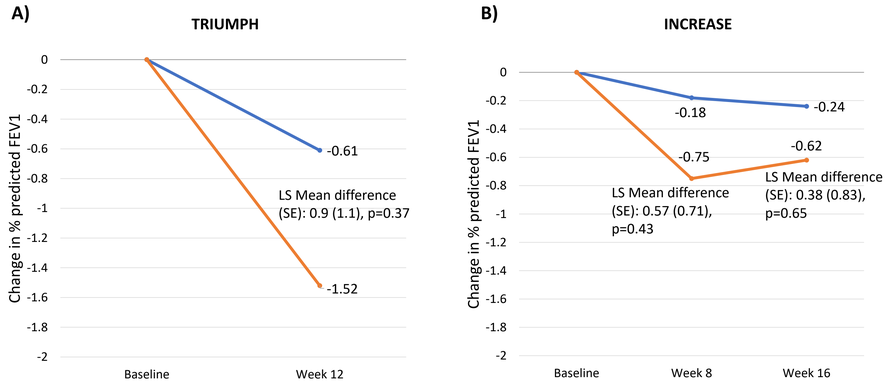


Figure 2: Change in lung function by visit: % predicted FEV1



DISCUSSION

- Results from this analysis suggests that PFT response to iTre in PAH differs mechanistically from PH-ILD. The significant improvements in % predicted FVC in patients with PH-ILD that is not observed in PAH suggest that the benefits of iTre may in part be attributed to improvements in lung disease rather than other hypothesized mechanisms such as improved PH or improved respiratory muscle function leading to increased FVC.

DISCUSSION (cont.)

- While numerically similar, FVC improvement in INCREASE may be evidence of treprostinil's antifibrotic effects that have previously been demonstrated in vitro.[3,4]
- Limitations of our analysis are the relatively short study durations, the differing time points for the evaluation of PFTs and the different statistical methodologies to evaluate change in the PFTs.

CONCLUSIONS

- The results of this post-hoc analysis suggest that PFT response to inhaled treprostinil in the INCREASE study may be evidence of an antifibrotic effect of inhaled treprostinil.
- Prospective studies in patients with ILD are needed to further investigate the antifibrotic effects of inhaled treprostinil. In this regard, consideration should be given to investigation of the safety and efficacy of inhaled treprostinil in patients with ILD in the absence of pulmonary hypertension.
- A clinical trial of inhaled treprostinil in patients with idiopathic pulmonary fibrosis (TETON, NCT04708782) is underway which will provide further information on the antifibrotic properties of inhaled treprostinil.

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CHEST 2021 ANNUAL MEETING | OCTOBER 17-20

Presented at CHEST 2021 Virtual
Disclosures: This study was sponsored by United Therapeutics Corporation.

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