The Safety and Efficacy of Inhaled Treprostinil in Patients with PH-ILD on Supplemental Oxygen: A Post-Hoc Analysis of the INCREASE Study

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INTRODUCTION

- INCREASE was a multicenter, randomized, double-blind, placebo-controlled, 16-week, parallel-group study. Inclusion criteria included diagnosis of pulmonary hypertension associated with interstitial lung disease (PH-ILD) by right heart catheterization and evidence of diffuse parenchymal lung disease on computed tomography imaging.
- The study met its primary endpoint of change in 6-minute walk distance (6MWD) at Week 16 as well as numerous secondary endpoints including change in N-terminal pro-brain natriuretic peptide (NT-proBNP) at Week 16 and time to clinical worsening.[1]
- The amount of supplemental oxygen required to maintain oxygen saturation (SpO2) at physiological levels is a common measure of disease severity for pulmonary diseases, as the degree of gas exchange impairment at rest is associated with higher mortality rates in idiopathic pulmonary fibrosis.[2]
- This post-hoc analysis evaluated the safety and efficacy of inhaled treprostinil (iTre) in patients on supplemental oxygen in INCREASE.

METHODS

- INCREASE study procedures and endpoints have been previously reported.[1] The study excluded patients on >10L/min of supplemental O_2.
- In this post-hoc analysis, patients in the INCREASE study were stratified by baseline supplemental O_2 into 3 groups: 0 L/min (no supplemental O_2), >0 to <4 L/min, and ≥4 L/min.
- To assess safety, adverse events (AEs), exacerbations, the frequency of patients who discontinued study drug, and oxygen saturation (SpO2) change during the 6MWT from baseline to Week 16 were compared between the three iTre groups using the Fisher's exact test and a mixed model for repeated measures (MMRM). The MMRM included change from baseline as the dependent variable; baseline desaturation, oxygen subgroup, visit, and oxygen subgroup x visit interaction as fixed effects; and subject as a random effect."
- Efficacy measures included the placebo-corrected difference in 6MWD and forced vital capacity (PVC) from baseline to Week 16.

RESULTS

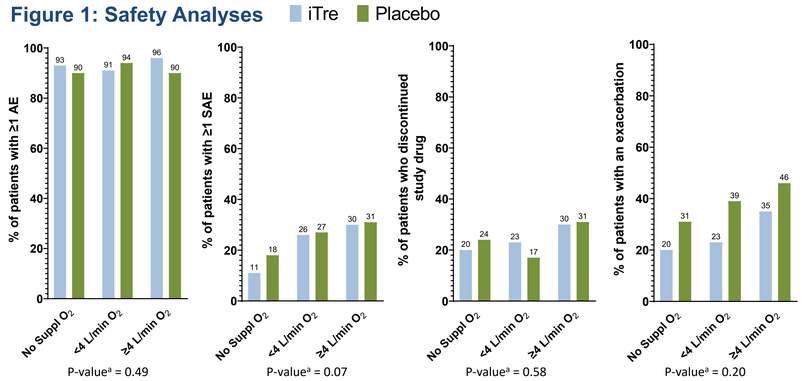
- Baseline characteristics varied between groups with those on higher rates of supplemental oxygen having lower 6MWD and higher BMI, pulmonary vascular resistance (PVR), and mean pulmonary arterial pressure (mPAP) [Table 1].
- There was no significant difference in the safety endpoints across the three iTre groups [Figure 1, Figure 2d]. In all 3 groups, exacerbations occurred in a smaller percentage of patients on iTre compared to patients on placebo."
- Participants in all three groups on inhaled treprostinil demonstrated improvements in 6MWD compared to those in the placebo groups [Figure 2]. Improvement in FVC among patients on inhaled treprostinil occurred in the 0 L/min and <4 L/min groups.

RESULTS (cont.)

Table 1: Baseline Characteristics

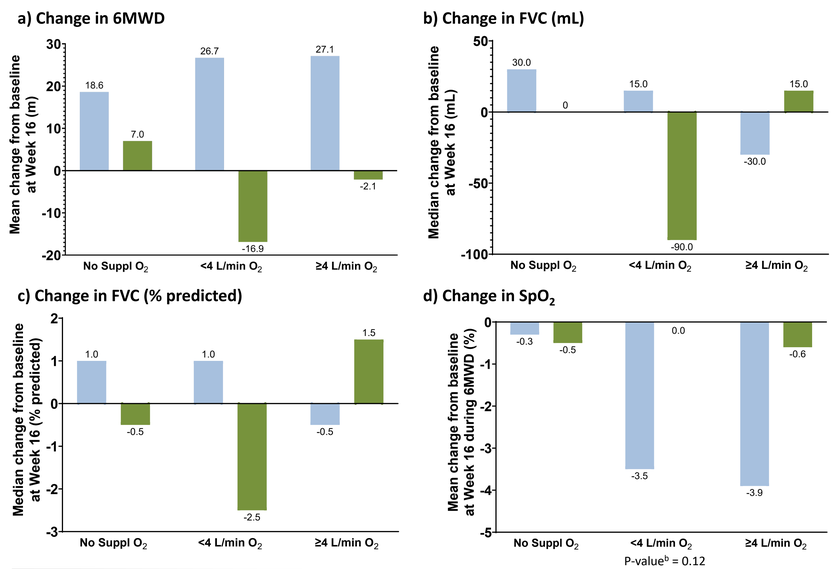
	No supplemental O_2		<4 L/min O_2		≥4 L/min O_2	
	iTre n = 44	Placebo n = 49	iTre n = 65	Placebo n = 66	iTre n = 54	Placebo n = 48
Age (mean ± SD), yrs	63.5 ± 12.9	64.8 ± 12.3	66.2 ± 13.2	67.3 ± 12.3	66.5 ± 12.0	70.2 ± 7.6
Sex, % female	50	45	55	36	50	46
BMI (mean ± SD), kg/m^2	28.4 ± 5.6	28.6 ± 5.6	29.6 ± 6.0	28.7 ± 6.0	31.6 ± 7.7	29.8 ± 6.0
6MWD (mean ± SD), m	333 ± 100	331 ± 87	235 ± 86	258 ± 74	212 ± 87	207 ± 80
NT-proBNP (median), pg/mL	228	321	816	411	674	646
Hemodynamics, median						
▪ PVR (WU)	5.4	4.7	5.7	5.2	6.1	5.5
▪ mPAP (mmHg)	32.5	32.0	37.0	35.0	37.0	36.5
▪ PCWP (mmHg)	9.0	10.0	10.0	9.5	11.0	10.0
Pulmonary function testing, median						
▪ FEV1, % predicted	64	63	62	65	63	64
▪ FVC, % predicted	59	60	60	61	62	60
▪ DLCO, % predicted	34	33	28	24	25	22
▪ TLC, % predicted	60	59	63	61	64	67

Figure 1: Safety Analyses



[a] P-values for AEs, SAEs, discontinuations, and exacerbations compare three inhaled treprostinil groups and are calculated using Fisher's exact test.
[b] P-values for SpO_2 are calculated using the F-test of equal mean changes, using MMRM.

Figure 2: 6MWD, FVC, and SpO_2



DISCUSSION

- This subgroup analysis of patients in the INCREASE study demonstrated the safety and efficacy of inhaled treprostinil in those patients who required supplemental oxygen.
- Participants with advanced disease, including those on ≥4 L/min of supplemental oxygen, derived benefit from inhaled treprostinil without significant changes in safety.
- Patients on inhaled treprostinil experienced some desaturation during the 6MWT but it was minimal. This desaturation should be considered in clinical context of the benefit of the drug, such as improved 6MWD[1], clinical worsening[1], and FVC[3].
- Furthermore, the benefits of inhaled treprostinil on 6MWD and FVC change were seen across all three subgroups, which is consistent with the primary results of the INCREASE study.

REFERENCES

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Poster 505 | Presented at ATS 2023 Annual Meeting | May 19-24, 2023 | Washington, DC
Disclosure: The INCREASE study was sponsored by United Therapeutics Corporation.

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