A Multicenter, Randomized, Double-Blinded, Placebo-Controlled Trial to Evaluate the Safety and Efficacy of Inhaled Treprostinil in Subjects with Pulmonary Hypertension due to Parenchymal Lung Disease (INCREASE Study)

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INTRODUCTION

- Pulmonary hypertension (PH) due to lung diseases and/or hypoxemia is classified by the World Health Organization (WHO) as WHO Group 3 PH. This classification includes PH due to interstitial lung disease (ILD) as well as combined pulmonary fibrosis and emphysema (CPFE).
- Interstitial lung disease encompasses a heterogeneous group of parenchymal lung diseases that are characterized by significant scarring or fibrosis of the bronchioles and alveolar sacs which prevents oxygenation and free gas exchange. The incidence of PH in ILD has been reported in up to 86% of patients and is associated with a poorer prognosis and decreased quality of life (QOL).
- Combined pulmonary fibrosis and emphysema is characterized by emphysema, fibrosis, and abnormalities of gas exchange. Up to 50% of CPFE patients have been reported to develop PH with increased PVR associated with a decreased survival.
- There are no approved treatments for PH in patients with ILD or CPFE; however, the results of some approved therapies for pulmonary arterial hypertension (PAH) have stimulated further investigation in these indications.
- Inhaled treprostinil has shown clinical improvements in exercise capacity after 12 weeks of therapy in patients with WHO Group 1 PH and directly targets the more ventilated portion of the lungs in patients with WHO Group 3 PH, minimizing the risk of ventilation perfusion mismatch, which may allow for improvements in exercise capacity.
- Faria-Urbina studied 22 patients with WHO Group 3 PH treated with inhaled treprostinil and followed up clinically for at least 3 months. The results suggest that inhaled treprostinil is well tolerated in patients with Group 3 PH and showed improvements in terms of functional class and exercise capacity without deleterious effects on gas exchange.[1]

OBJECTIVE

- The purpose of the INCREASE study is to evaluate the safety and efficacy of inhaled treprostinil in subjects with PH associated with ILD including CPFE.

METHODS

Study Design

- INCREASE is a 16-week, Phase III, multicenter, randomized double-blind, placebo controlled study.
- The study will include about 314 patients who will initiate inhaled treprostinil or placebo at a dose of 3 breaths 4 times daily up to a target of 9 breaths 4 times daily and a maximum dose of 12 breaths 4 times daily, as clinically tolerated.
- The primary efficacy endpoint of the study is the change in 6-minute walk distance (6MWD) at Week 16. Additional key assessments during the study include change in peak 6MWD at Week 12, trough 6MWD at Week 15, and change in plasma concentration of N-terminal probrain natriuretic peptide (NT-proBNP).
- Optional blood samples for evaluation of biomarkers and pharmacogenomics will also be drawn in subjects providing consent.
- Patients who complete all required assessments will be eligible to enter an open-label, extension study.

Analysis

- Baseline demographics for 147 randomized study subjects have been combined as an interim characterization of the study population.
- Correlations between baseline lung function and hemodynamics have been provided for parameters collected at baseline or within 1 year of randomization.

RESULTS

- The interim cut of 147 subjects includes 70 (48%) females and 77 (52%) males with a mean age of 67 years (range, 29-89).
- Baseline 6MWD was 253 meters (range, 100-533) and 118 patients (82%) were receiving supplemental oxygen at an average flow rate of 5.74 L/m.

RESULTS (cont'd)

- Mean body mass index at baseline is 29.5 kg/m2 (range, 14-52.9).
- At baseline 11 patients (7%) were using nintedanib and 19 patients(13%) were using pirfenidone.
- The underlying disease etiology is shown in Figure 1.

Table 1. Hemodynamic Eligibility Criteria (within 1 year of Randomization)

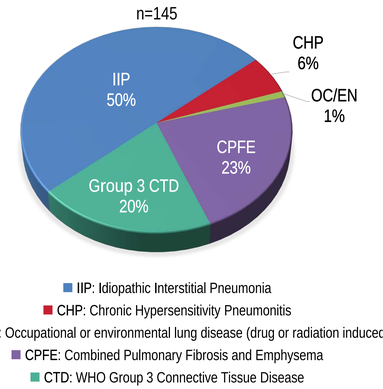
Parameter (n=146)	Value (range)
Mean pulmonary artery pressure, mmHg	37.34 (25-74)
Pulmonary capillary wedge pressure, mmHg	10.32 (3-20)
Pulmonary vascular resistance, WU	6.44 (3.06-16.5)

Table 2. Pulmonary Function Test Values at Baseline

Pulmonary Function Parameter (% predicted)	Mean (range)
FEV1 (n=142)	63.89 (22-122)
FVC (n=142)	62.56 (20-130)
TLC (n=135)	65.22 (28-126)
DLCO (n=133)	30.11 (1-86)

FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; TLC, total lung capacity; DLCO, lung diffusion capacity

Figure 1. Disease Etiology



Interim Results: Several correlations of baseline demographics were evaluated and only three were found to be statistically significant.

- There was a significant negative correlation between DLCO and PVR (r=-0.26058, p=0.0025). [Figure 2]
- There was a significant negative correlation between 6MWD and PVR (r=-0.34940, p<0.0001). [Figure 3]
- There was a significant negative correlation between 6MWD and mPAP (r=-0.35387, p<0.0001). [Figure 4]

Figure 2. DLCO and PVR

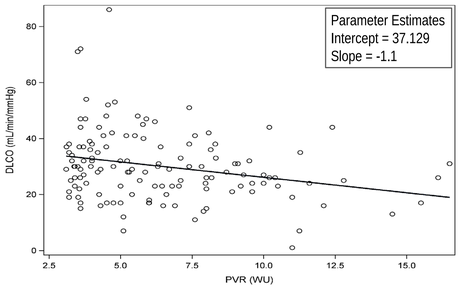


Figure 3. Walk Distance and PVR

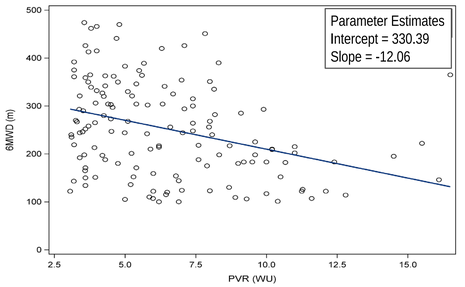
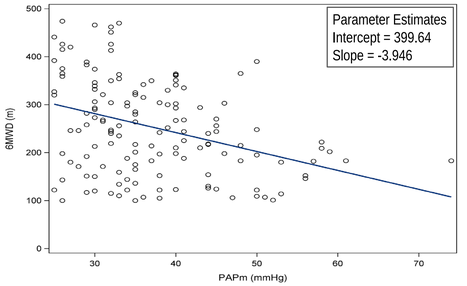


Figure 4. Walk Distance and PAPm



LIMITATIONS

- The Right Heart catheter parameters were collected as part of determining subject eligibility for enrollment. These values could have been up to 1 year prior to randomization.

CONCLUSIONS

- Enrollment is ongoing at approximately 115 sites in the United States and is anticipated to continue through 2018 or until all 314 subjects have been enrolled into the double-blind phase of the trial.

REFERENCES

1. Faria-Urbina M, Oliveira RKF, Agarwal M, Waxman AB (2018) Inhaled Treprostinil in Pulmonary Hypertension Associated with Lung Disease. *Lung* 196:139–146.

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