ORIGINAL ARTICLE

# Inhaled Treprostinil in Pulmonary Hypertension Due to Interstitial Lung Disease

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## ABSTRACT

### BACKGROUND

No therapies are currently approved for the treatment of pulmonary hypertension in patients with interstitial lung disease. The safety and efficacy of inhaled treprostinil for patients with this condition are unclear.

### METHODS

We enrolled patients with interstitial lung disease and pulmonary hypertension (documented by right heart catheterization) in a multicenter, randomized, double-blind, placebo-controlled, 16-week trial. Patients were assigned in a 1:1 ratio to receive inhaled treprostinil, administered by means of an ultrasonic, pulsed-delivery nebulizer in up to 12 breaths (total, 72 $\mu$g) four times daily, or placebo. The primary efficacy end point was the difference between the two groups in the change in peak 6-minute walk distance from baseline to week 16. Secondary end points included the change in N-terminal pro–B-type natriuretic peptide (NT-proBNP) level at week 16 and the time to clinical worsening.

### RESULTS

A total of 326 patients underwent randomization, with 163 assigned to inhaled treprostinil and 163 to placebo. Baseline characteristics were similar in the two groups. At week 16, the least-squares mean difference between the treprostinil group and the placebo group in the change from baseline in the 6-minute walk distance was 31.12 m (95% confidence interval [CI], 16.85 to 45.39; P<0.001). There was a reduction of 15% in NT-proBNP levels from baseline with inhaled treprostinil as compared with an increase of 46% with placebo (treatment ratio, 0.58; 95% CI, 0.47 to 0.72; P<0.001). Clinical worsening occurred in 37 patients (22.7%) in the treprostinil group as compared with 54 patients (33.1%) in the placebo group (hazard ratio, 0.61; 95% CI, 0.40 to 0.92; P=0.04 by the log-rank test). The most frequently reported adverse events were cough, headache, dyspnea, dizziness, nausea, fatigue, and diarrhea.

### CONCLUSIONS

In patients with pulmonary hypertension due to interstitial lung disease, inhaled treprostinil improved exercise capacity from baseline, assessed with the use of a 6-minute walk test, as compared with placebo. (Funded by United Therapeutics; INCREASE ClinicalTrials.gov number, NCT02630316.)

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Precapillary pulmonary hypertension is defined as an elevation in mean pulmonary arterial pressure and pulmonary vascular resistance.[1] In the World Health Organization (WHO) classification of pulmonary hypertension, precapillary pulmonary hypertension due to lung disease is classified as group 3. The most common lung diseases associated with group 3 pulmonary hypertension are chronic obstructive pulmonary disease and interstitial lung disease.

Pulmonary hypertension has been reported in up to 86% of patients with interstitial lung disease and is associated with reduced exercise capacity, greater need for supplemental oxygen, decreased quality of life, and earlier death.[2-4] Despite the global prevalence and poor clinical course of pulmonary hypertension due to interstitial lung disease, there are currently no approved therapies for these patients. Although data are limited, therapies approved for group 1 pulmonary hypertension (pulmonary arterial hypertension) have been used to treat group 3 pulmonary hypertension.[5] Previous studies of vasodilator therapies have shown conflicting results. The largest trial to date evaluated the soluble guanylate cyclase stimulator riociguat in a patient population with group 3 pulmonary hypertension and was stopped early owing to serious harm.[6]

Treprostinil is a stable analogue of prostacyclin, which promotes direct vasodilation of pulmonary and systemic arterial vascular beds and inhibits platelet aggregation.[7] An inhaled formulation of treprostinil was previously shown to improve exercise capacity after 12 weeks of therapy in patients with group 1 pulmonary hypertension.[8] Data from previously completed pilot studies suggest that inhaled treprostinil can improve hemodynamics and functional capacity in patients with group 3 pulmonary hypertension.[9-12] Therefore, the objective of the INCREASE trial was to evaluate the safety and efficacy of inhaled treprostinil in patients with pulmonary hypertension due to interstitial lung disease.

## Methods

### Trial Design and Oversight

INCREASE was a multicenter, randomized, double-blind, placebo-controlled trial. The steering committee (the first author and last two authors), in collaboration with the trial sponsor (United Therapeutics), designed the trial and oversaw its conduct. The trial protocol (available with the full text of this article at NEJM.org) was approved by the institutional review board at each participating site. The trial was monitored by an independent data and safety monitoring committee and was conducted in accordance with Good Clinical Practice guidelines. A full list of trial personnel, including the investigators and trial committees, is provided in Section S1 in the Supplementary Appendix, available at NEJM.org.

The collection, management, and analysis of the data were performed by the sponsor according to a prespecified statistical analysis plan (provided in the protocol). An independent academic statistician reviewed the statistical analysis plan and confirmed the primary efficacy analyses. Authors had independent access to the data and authority to conduct and confirm statistical analyses. All manuscript drafts were written by the steering committee and authors affiliated with the sponsor and were reviewed and approved by all the authors. The authors assume responsibility for the accuracy and completeness of the data, as well as for the fidelity of the trial to the protocol.

### Trial Population

The trial population consisted of patients 18 years of age or older in whom interstitial lung disease was diagnosed on the basis of evidence of diffuse parenchymal lung disease on computed tomography of the chest (not centrally adjudicated) performed within 6 months before randomization. Confirmation of group 3 pulmonary hypertension by right heart catheterization within 1 year before randomization was required. Group 3 pulmonary hypertension was defined by pulmonary vascular resistance of more than 3 Wood units, pulmonary capillary wedge pressure of 15 mm Hg or lower, and mean pulmonary arterial pressure of 25 mm Hg or higher. Patients with group 3 pulmonary hypertension due to connective tissue disease were also required to have a baseline forced vital capacity of less than 70%. Eligible patients also had to walk at least 100 m during a 6-minute walk test. Patients receiving drug treatment (i.e., pirfenidone or nintedanib) for their underlying lung disease were required to have been receiving a stable dose for at least 30 days before undergoing randomization. Patients re-

ceiving approved therapy for pulmonary arterial hypertension within 60 days before randomization were not eligible for enrollment. A complete list of trial enrollment criteria is provided in Section S2. Written informed consent was obtained from all the patients.

### TRIAL PROCEDURES

Within 30 days after screening, eligible patients were randomly assigned in a 1:1 ratio to receive inhaled treprostinil (Tyvaso, United Therapeutics) or placebo in a double-blind manner. Randomization, based on permuted blocks, was stratified by baseline 6-minute walk distance (≤350 m vs. >350 m) and was implemented through an interactive Web-response system.

Inhaled treprostinil (0.6 mg per milliliter) was administered by means of an ultrasonic, pulsed-delivery nebulizer at 6 μg per breath. Placebo was administered similarly as a visually identical solution. The first dose of trial drug (3 breaths) was administered in the clinic, followed by at least a 1-hour observation period. The dose of treprostinil or placebo was adjusted, with dose escalation (an additional 1 breath four times daily) occurring as often as every 3 days, with a target dose of 9 breaths four times daily and a maximum dose of 12 breaths four times daily. Investigators adjusted the dose on an individual patient basis to achieve the maximum tolerated dose leading to functional improvement.

### TRIAL ASSESSMENTS

The 6-minute walk test was performed and laboratory data were obtained at baseline and at weeks 4, 8, 12, and 16, or at the time of early discontinuation of treprostinil or placebo. Each 6-minute walk test was performed 10 to 60 minutes after the most recent dose of active drug or placebo, which is the time of peak plasma treprostinil exposure. (A description of the procedure for the 6-minute walk test is provided in Section S3.) A trough test was performed at week 15 at least 4 hours after the participant received a dose of treprostinil or placebo and at least 24 hours before the week 16 test. Pulse oximetry was performed immediately before, during, and after each 6-minute walk test. Measurement of N-terminal pro–B-type natriuretic peptide (NT-proBNP) levels and pulmonary function tests were performed at baseline and at weeks 8 and 16 (or at early discontinuation) after the patients recovered from the 6-minute walk test. The St. George's Respiratory Questionnaire (SGRQ), a quality-of-life measure, was completed at baseline and week 16 or at the time of early discontinuation.

### OUTCOME MEASURES

The primary end point of the trial was the difference between the two groups in the change in peak 6-minute walk distance from baseline to week 16. Secondary efficacy end points were analyzed in the following hierarchical testing order: the change in NT-proBNP level from baseline to week 16, the time to clinical worsening, the change in 6-minute walk distance at peak plasma treprostinil level at week 12, and the change in 6-minute walk distance at trough treprostinil level at week 15. The time to clinical worsening was evaluated from the time of randomization until the patient's withdrawal from the trial and was defined as the time until the occurrence of any one of the following events: hospitalization for a cardiopulmonary indication, a decrease in 6-minute walk distance greater than 15% from baseline that was directly related to the disease under study at two consecutive visits and at least 24 hours apart, death from any cause, or lung transplantation.

Exploratory end points were the changes in peak 6-minute walk distance at weeks 4 and 8, quality of life as measured with the use of the SGRQ at week 16, and the distance–saturation product (calculated by multiplying the total distance walked by the lowest oxygen saturation measurement during the 6-minute walk) at week 16. Safety end points included adverse events, abnormal laboratory results, oxygenation as measured by pulse oximetry ($Spo_2$) and supplemental oxygen requirement, changes in pulmonary function test results, hospitalization for a cardiopulmonary indication, and investigator-reported exacerbations of underlying lung disease, defined as acute, clinically significant respiratory deterioration characterized by evidence of new widespread alveolar abnormality. A full list of trial end points is provided in Section S4.

### STATISTICAL ANALYSIS

Original estimates suggested that with 266 patients randomly assigned in a 1:1 ratio to receive

inhaled treprostinil or placebo, the trial would have at least 90% power at a significance level of 0.05 (two-sided) to detect a between-group difference of 30 m in the change in peak 6-minute walk distance from baseline at week 16, assuming a standard deviation of 75 m. To account for approximately 15% of participants discontinuing the trial, 314 patients would need to be enrolled.

For the primary efficacy analysis, the change in 6-minute walk distance was analyzed by mixed-model repeated-measures methods, under the assumption that missing data were missing at random. The model included the change from baseline to peak 6-minute walk distance as the dependent variable, with treatment, week, and treatment-by-week interaction as fixed effects, and the baseline 6-minute walk distance as a covariate. A sensitivity analysis for the primary end point was performed by means of a multiple imputation approach with a multivariate normal imputation model according to the Markov chain Monte Carlo method. The imputation model included treatment group, all scheduled visits, the patient's sex, and the patient's age at randomization. If the result for the primary efficacy end point was significant, secondary efficacy end points were to be evaluated according to a hierarchical testing procedure. Confidence intervals have not been adjusted for multiplicity and cannot be used to infer definitive treatment effects for secondary efficacy end points. Additional details of the statistical methods are provided in Section S5.

## RESULTS

### PATIENTS

Of 462 patients screened for eligibility, 326 were enrolled at 93 centers from February 3, 2017, through August 30, 2019, and were randomly assigned to receive placebo (163 patients) or inhaled treprostinil (163 patients) (Fig. 1). Reasons for screening failure for the 136 patients who were excluded are shown in Table S1. Baseline characteristics were similar in the two groups (Table 1). The mean age of the patients was 66.5 years, 46.9% were female, and the most common diagnosis was idiopathic interstitial pneumonia (in 44.8%). Baseline test data are provided in Table S2. At baseline, the mean 6-minute walk distance was 259.6 m, the mean pulmonary vascular resistance was 6.2 Wood units, and the mean NT-proBNP level was 1832.9 pg per milliliter.

### EXPOSURE AND FOLLOW-UP

Patients in the treprostinil group took a median of 11 breaths from the inhaler (66 μg) at each of four daily sessions at week 12 and 12 breaths (72 μg) per session at week 16. The percentage of patients in this group who took 10 to 12 breaths (60 to 72 μg) per session was 57.0% at week 12 and 57.8% at week 16. Patients in the placebo group took a median of 12 breaths from the inhaler per session at weeks 12 and 16.

The date of the database lock was February 18, 2020. Forty patients assigned to receive inhaled treprostinil (24.5%) and 38 assigned to placebo (23.3%) discontinued the assigned regimen prematurely. These patients were encouraged to remain in the trial and complete assessments through week 16; 33 patients in the treprostinil group and 35 in the placebo group discontinued participation in the trial. The reasons for discontinuation are shown in Figure 1.

### PRIMARY END POINT

Mean within-group changes in the 6-minute walk distance are shown in Figure 2. Mixed-model repeated-measures analysis showed that the least-squares mean difference between the treprostinil group and the placebo group in the change from baseline in peak 6-minute walk distance was 31.12 m (95% confidence interval [CI], 16.85 to 45.39; P<0.001) (Table 2 and Fig. S1). Similar effects were observed across subgroups, including subgroups defined by disease cause and severity (as measured by baseline 6-minute walk distance), baseline hemodynamics, and dose group (Fig. S2). In addition, the between-group difference in the change from baseline in peak 6-minute walk distance at week 16 was significant when analyzed with multiple imputation according to the Markov chain Monte Carlo method (30.97 m; 95% CI, 16.53 to 45.41; P<0.001) (Fig. S3).

### SECONDARY AND EXPLORATORY END POINTS

Patients assigned to inhaled treprostinil, as compared with those assigned to placebo, showed significant improvements in each of the secondary end points (Table 2). The NT-proBNP level decreased 15% from baseline with inhaled treprostinil and increased 46% from baseline with

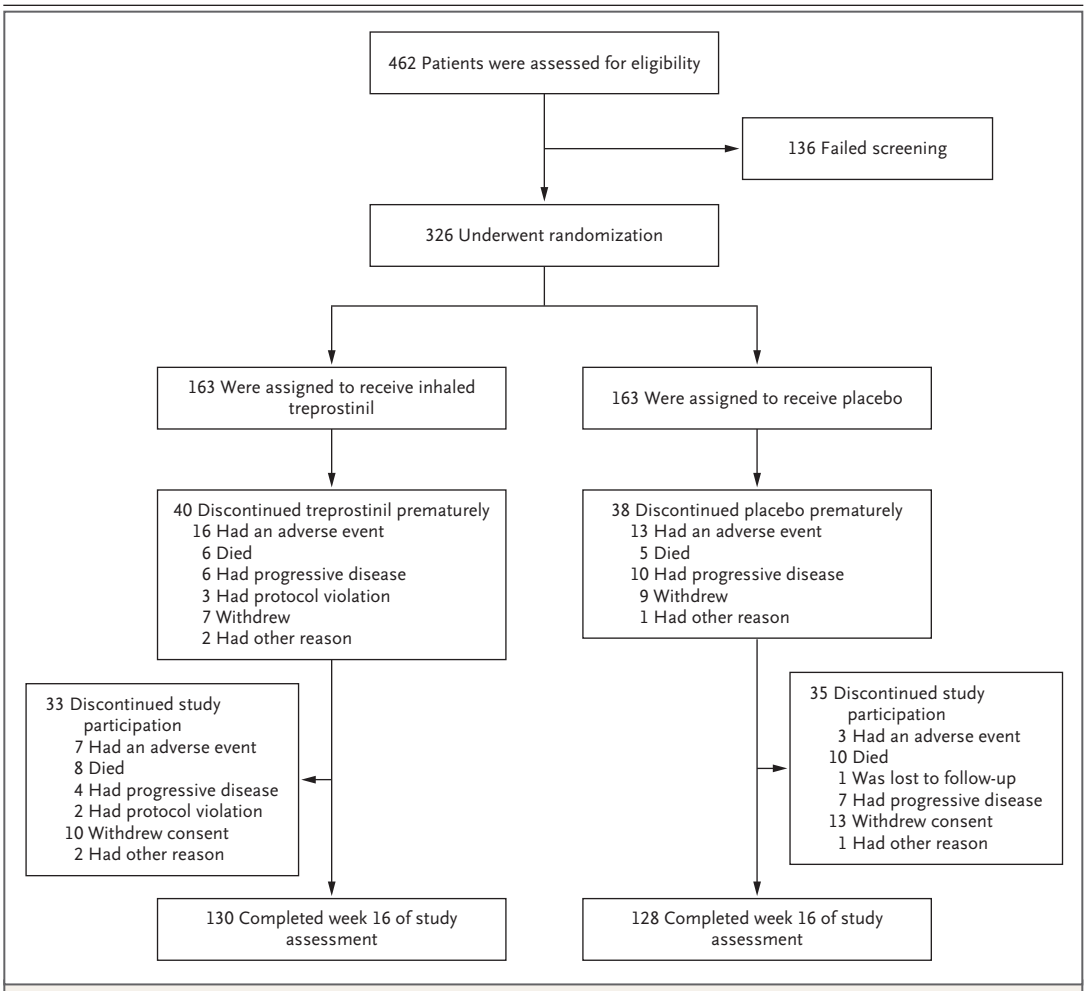


**Figure 1. Screening, Randomization, and Follow-up.**

Of 462 patients screened for eligibility, 326 patients underwent randomization and received at least one dose of the assigned treprostinil or placebo (included in the intention-to-treat and safety populations). Reasons for screening failure (136 patients) are shown in Table S1. Of the patients who underwent randomization, 40 patients in the treprostinil group and 38 in the placebo group discontinued the assigned regimen prematurely. These patients were not withdrawn from the trial but were encouraged to remain and complete assessments through week 16; 33 patients in the treprostinil group and 35 in the placebo group discontinued trial participation before week 16.

placebo, as assessed by the least-squares mean for the log-transformed ratio to the baseline level at week 16 (treatment ratio, 0.58; 95% CI, 0.47 to 0.72; P<0.001) (Fig. S4). Clinical worsening occurred in 37 patients (22.7%) in the treprostinil group, as compared with 54 patients (33.1%) in the placebo group (hazard ratio, 0.61; 95% CI, 0.40 to 0.92; P=0.04 by the log-rank test) (Fig. S5). The least-squares mean change from baseline to week 12 in peak 6-minute walk distance was 31.29 m greater in the treprostinil group than in the placebo group (P<0.001), and the change from baseline to week 15 in trough 6-minute walk distance was 21.99 m greater in the treprostinil group (P=0.004). There was no significant between-group difference in patient-reported quality of life as assessed with the SGRQ or in the distance–saturation product at week 16 (Tables S3 and S4).

### SAFETY END POINTS

The most frequently reported adverse events were cough, headache, dyspnea, dizziness, nausea, fatigue, and diarrhea (Table 3). Most of these

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