ORIGINAL ARTICLE

Inhaled Treprostinil in Pulmonary Hypertension Due to Interstitial Lung Disease

Aaron Waxman, M.D., Ph.D., Ricardo Restrepo-Jaramillo, M.D., Thenappan Thenappan, M.D., Ashwin Ravichandran, M.D., Peter Engel, M.D., Abubakr Bajwa, M.D., Roblee Allen, M.D., Jeremy Feldman, M.D., Rahul Argula, M.D., Peter Smith, Pharm.D., Kristan Rollins, Pharm.D., Chunqin Deng, M.D., Ph.D., Leigh Peterson, Ph.D., Heidi Bell, M.D., Victor Tapson, M.D., and Steven D. Nathan, M.D.

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 μg) 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.)

From Brigham and Women's Hospital, Boston (A.W.); the University of South Florida, Tampa (R.R.-J.), and St. Vincent's Lung, Sleep, and Critical Care Specialists, Jacksonville (A.B.) — both in FL; the University of Minnesota, Minneapolis (T.T.); St. Vincent Medical Group, Indianapolis (A.R.); the Carl and Edyth Lindner Research Center at the Christ Hospital, Cincinnati (P.E.); University of California Davis Medical Center, Sacramento (R. Allen), and Cedars–Sinai, Los Angeles (V.T.); Arizona Pulmonary Specialists, Phoenix (J.F.); the Medical University of South Carolina, Charleston (R. Argula); United Therapeutics Corporation, Silver Spring, MD (P.S., K.R., C.D., L.P., H.B.); and Inova Fairfax Hospital, Falls Church, VA (S.D.N.). Address reprint requests to Dr. Nathan at the Advanced Lung Disease and Lung Transplant Program, Inova Heart and Vascular Institute, 3300 Gallows Rd., Falls Church, VA 22042, or at steven.nathan@inova.org.

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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 receiving 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 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 oc-

curred 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 events were of mild-to-moderate intensity. Serious adverse events occurred in 23.3% of the patients who received inhaled treprostinil and in 25.8% of those who received placebo (Table S5).

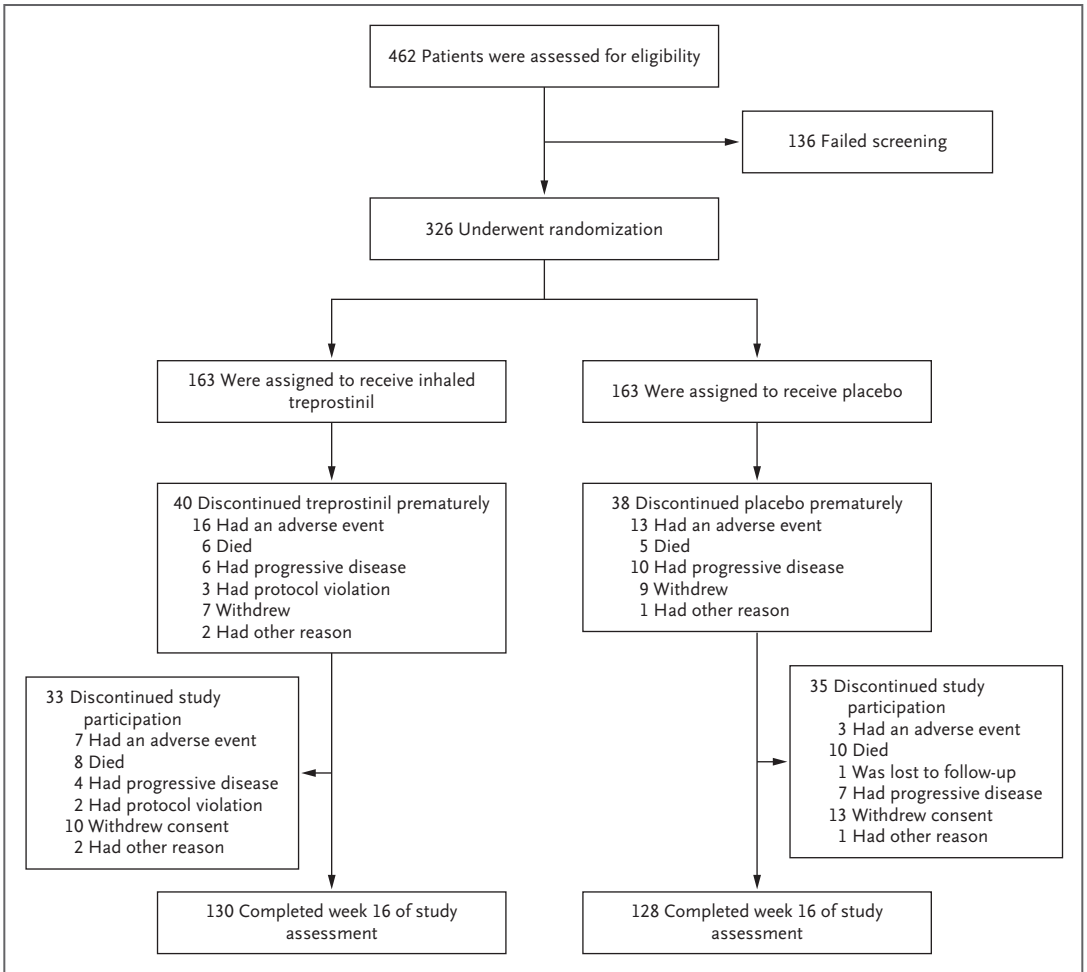

Figure 1. Screening, Randomization, and Follow-up.

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.

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Inhaled Treprostinil (N=163)	Placebo (N=163)	All Patients (N=326)
Female sex — no. (%)	85 (52.1)	68 (41.7)	153 (46.9)
Mean age at randomization (range) — yr	65.6 (26–90)	67.4 (36–85)	66.5 (26–90)
Age distribution — no. (%)			
<65 yr	64 (39.3)	48 (29.4)	112 (34.4)
65 to <80 yr	83 (50.9)	100 (61.3)	183 (56.1)
≥80 yr	16 (9.8)	15 (9.2)	31 (9.5)
Race or ethnic group — no. (%)†			
White	112 (68.7)	126 (77.3)	238 (73.0)
Black or African American	41 (25.2)	30 (18.4)	71 (21.8)
American Indian or Alaska Native	2 (1.2)	1 (0.6)	3 (0.9)
Asian	7 (4.3)	5 (3.1)	12 (3.7)
Multiple	0	1 (0.6)	1 (0.3)
Unknown	1 (0.6)	0	1 (0.3)
Hispanic or Latino ethnic group — no. (%)†			
Yes	11 (6.7)	16 (9.8)	27 (8.3)
No	152 (93.3)	146 (89.6)	298 (91.4)
Data missing	0	1 (0.6)	1 (0.3)
Mean time since diagnosis — yr	0.54±1.16	0.54±1.31	0.54±1.23
Cause of lung disease — no. (%)			
Idiopathic interstitial pneumonia	65 (39.9)	81 (49.7)	146 (44.8)
Chronic hypersensitivity pneumonitis	10 (6.1)	9 (5.5)	19 (5.8)
Occupational lung disease	5 (3.1)	1 (0.6)	6 (1.8)
Combined pulmonary fibrosis and emphysema	42 (25.8)	40 (24.5)	82 (25.2)
Connective tissue disease	40 (24.5)	32 (19.6)	72 (22.1)
Other	1 (0.6)	0	1 (0.3)
Idiopathic interstitial pneumonia subcategory — no. (%)			
Idiopathic pulmonary fibrosis	37 (22.7)	55 (33.7)	92 (28.2)
Idiopathic nonspecific interstitial pneumonia	21 (12.9)	16 (9.8)	37 (11.3)
Respiratory bronchiolitis associated with interstitial lung disease	2 (1.2)	0	2 (0.6)
Desquamative interstitial pneumonia	0	1 (0.6)	1 (0.3)
Acute interstitial pneumonia	0	1 (0.6)	1 (0.3)
Unclassified idiopathic interstitial pneumonia	5 (3.1)	8 (4.9)	13 (4.0)
Use of supplemental oxygen — no. (%)	119 (73.0)	114 (69.9)	233 (71.5)
Background therapy — no. (%)			
None	133 (81.6)	119 (73.0)	252 (77.3)
Pirfenidone only	19 (11.7)	25 (15.3)	44 (13.5)
Nintedanib only	11 (6.7)	19 (11.7)	30 (9.2)

* Plus–minus values are means ±SD. Additional patient characteristics at baseline are provided in Table S2 in the Supplementary Appendix. Percentages may not total 100 because of rounding.
† Race and ethnic group were reported by the patient.

No serious adverse events were reported significantly more frequently in the treprostinil group than in the placebo group. A full list of serious adverse events is provided in Table S5.

Significantly fewer patients in the treprostinil group than in the placebo group had exacerbations of underlying lung disease (43 [26.4%] vs. 63 [38.7%]; P=0.02 by Fisher's exact test). Fewer patients in the treprostinil group than in the placebo group had a first occurrence of clinical worsening that involved hospitalization for a cardiopulmonary indication (18 [11.0%] vs. 24 [14.7%]; P=0.41). Inhaled treprostinil had no deleterious effect on any pulmonary function test variable during the trial (Table S6). There were no significant treatment-related changes in pulse oximetry or supplemental oxygen use in either group over the trial period (Tables S7 and S8).

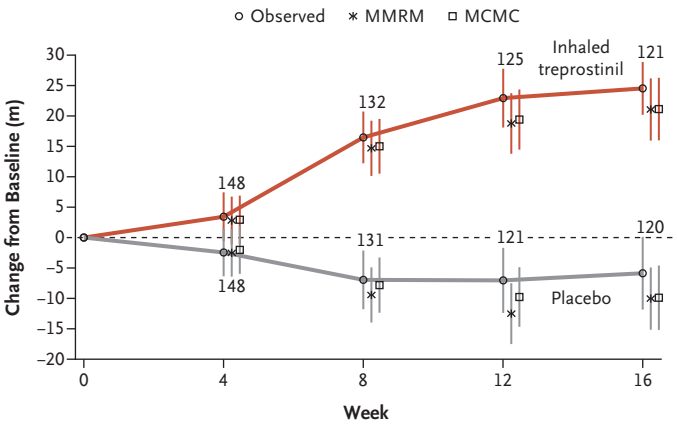

Figure 2. Mean Change from Baseline in Peak 6-Minute Walk Distance through Week 16.

Shown are mean (±SE) changes from baseline (dashed line) in peak 6-minute walk distance over the 16-week trial period. The data shown are for patients with available data (observed) as well as for the results of two analysis methods used to account for missing data. The values shown at each data point indicate the number of patients assessed at that time point. The primary analysis used mixed-model repeat-measurement (MMRM) methods, with 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 with the use of a multiple imputation approach with a multivariate normal imputation model using the Markov chain Monte Carlo (MCMC) method. The imputation model included treatment group, all scheduled visits, patient's sex, and patient's age at randomization. The confidence intervals have not been adjusted for multiplicity and cannot be used to infer definitive treatment effects.

DISCUSSION

Pulmonary hypertension frequently complicates the treatment of patients with interstitial lung disease and is associated with worse functional status, greater need for supplemental oxygen, and worse outcomes.[3,13] In the INCREASE trial, patients treated with inhaled treprostinil had significant improvements in exercise capacity, as evidenced by changes in the 6-minute walk distance. Treatment with inhaled treprostinil was also associated with a lower risk of clinical worsening than that in patients who received placebo, as well as reductions in NT-proBNP levels and fewer exacerbations of underlying lung disease, over the 16-week treatment period. The safety profile of inhaled treprostinil observed in this vulnerable patient population was similar to that reported in previous studies. The most frequently reported adverse events were cough, headache, dyspnea, dizziness, nausea, fatigue, and diarrhea. The use of inhaled treprostinil was not associated with any decrement in lung function.

Patients with group 3 pulmonary hypertension are often treated with systemic pulmonary vasodilators, which are currently approved only for treatment of group 1 pulmonary hypertension. However, there is concern that such agents could worsen ventilation–perfusion matching in patients with group 3 pulmonary hypertension. Inhaled agents have the advantage of preferentially redirecting blood flow to the best-ventilated lung units, thus reducing the risk of ventilation–perfusion mismatching.[9,14] Indeed, a retrospective study of inhaled treprostinil in patients with group 3 pulmonary hypertension showed that such patients had improvements in functional class and 6-minute walk distance without any adverse effect on peripheral oxygen saturation, reinforcing the concept of unchanged or even improved ventilation–perfusion matching with inhaled treprostinil.[10] Similarly, in the current trial, we found no evidence of worsened oxygenation, which further allays concerns about ventilation–perfusion mismatching.

The INCREASE trial was not without its limitations. The trial was of short duration, and 21% of the patients discontinued the trial prematurely

Table 2. Summary of Primary and Secondary End Points.*

End Point	Inhaled Treprostinil (N=163)	Placebo (N=163)	Treatment Effect (95% CI)	P Value
Primary end point				
Change in peak 6-minute walk distance from baseline to wk 16 — m†	21.08±5.12	−10.04±5.12	31.12±7.25 (16.85 to 45.39)‡	<0.001
Secondary end points§				
Change in plasma concentration of NT-proBNP from baseline to wk 16¶				
Mean (±SD) change — pg/ml	−396.35±1904.90	1453.95±7296.20		
Median — pg/ml	−22.65	20.65		
Range — pg/ml	−11,433.0 to 5373.1	−5483.3 to 87,148.3		
Ratio to baseline	0.85±0.06	1.46±0.11	0.58±0.06 (0.47 to 0.72)‖	<0.001
Occurrence of clinical worsening — no. (%)			0.61 (0.4 to 0.92)**	0.04
Any event	37 (22.7)	54 (33.1)		
Hospitalization for cardiopulmonary indication	18 (11.0)	24 (14.7)		
Decrease in 6-minute walk distance of >15% from baseline	13 (8.0)	26 (16.0)		
Death from any cause	4 (2.5)	4 (2.5)		
Lung transplantation	2 (1.2)	0		
Least-squares mean change in peak 6-minute walk distance from baseline to wk 12 — m†	18.77±4.99	−12.52±5.01	31.29±7.07 (17.37 to 45.21)‡	<0.001
Least-squares mean change in trough 6-minute walk distance from baseline to wk 15 — m	9.3±5.5	−12.7±5.5	21.99±7.7 (6.85 to 37.14)‡	0.005††

* Plus–minus values are means ±SE, unless otherwise indicated. For secondary end points, the confidence intervals (CIs) have not been adjusted for multiplicity and cannot be used to infer definitive treatment effects. NT-proBNP denotes N-terminal pro–B-type natriuretic peptide.

† The effect of inhaled treprostinil as compared with placebo on the change in 6-minute walk distance was evaluated with the use of a mixed-model repeat measurement with the change from baseline in peak 6-minute walk distance as the dependent variable; treatment, week, and treatment-by-week interaction as the fixed effects; baseline 6-minute walk distance as the covariate; and subject as the random effect. Results are shown in Figures S1 and S3.

‡ This is a least-squares mean difference between the groups.

§ The effect of inhaled treprostinil as compared with placebo on the change in log-transformed NT-proBNP was evaluated with the use of a mixed-model repeat measurement with the change from baseline in log-transformed NT-proBNP as the dependent variable; treatment, week, and treatment-by-week interaction as the fixed effects; and log-transformed baseline NT-proBNP as the covariate. Ratio to baseline is the least-squares mean of the change from baseline in log-transformed data.

¶ The change in plasma concentration of NT-proBNP from baseline to week 16 was assessed in 156 patients in the treprostinil group and 160 in the placebo group.

‖ This is the treatment ratio, which is the ratio of ratios between two treatment groups.

** This is a hazard ratio, calculated from a Cox proportional-hazards model. The P value was calculated with the use of a log-rank test stratified by the baseline 6-minute walk distance category.

†† The P value was obtained from 100 multiple imputations with Markov chain Monte Carlo estimation with the use of analysis of covariance (ANCOVA) modeling, with the change from baseline in peak 6-minute walk distance as the dependent variable, treatment as a fixed effect, and baseline 6-minute walk distance as a covariate.

(before week 16). In addition, events of clinical worsening and exacerbation of underlying lung disease were investigator-reported and not adjudicated by an independent review committee. Finally, the size of the favorable treatment effect on the 6-minute walk distance with inhaled treprostinil is similar to estimates of the minimum clinically important difference for this test in patients with pulmonary disease (21.7 to 37 m in a study by Nathan et al., and 24 to 45 m in a study by du Bois et al.).[15,16]

This study showed that among patients with pulmonary hypertension due to interstitial lung disease, treatment with inhaled treprostinil improved exercise capacity as shown by improvement in the 6-minute walk distance through the end of the 16-week treatment period. In addition, treatment with inhaled treprostinil was associated

Table 3. Summary of Adverse Events.

Variable	Inhaled Treprostinil (N=163)	Placebo (N=163)	P Value*
Total no. of adverse events	890	793	
Patients with ≥1 adverse event — no. (%)	152 (93.3)	149 (91.4)	0.68
Total no. of serious adverse events†	53	89	
Patients with ≥1 serious adverse event — no. (%)	38 (23.3)	42 (25.8)	0.70
Total no. of adverse events leading to withdrawal of treprostinil or placebo	47	38	
Most frequently occurring adverse events — no. of patients (%)‡			
Cough	71 (43.6)	54 (33.1)	0.07
Headache	45 (27.6)	32 (19.6)	0.12
Dyspnea	41 (25.2)	51 (31.3)	0.27
Dizziness	30 (18.4)	23 (14.1)	0.37
Nausea	25 (15.3)	26 (16.0)	>0.99
Fatigue	23 (14.1)	23 (14.1)	>0.99
Diarrhea	22 (13.5)	19 (11.7)	0.74
Throat irritation	20 (12.3)	6 (3.7)	0.007
Oropharyngeal pain	18 (11.0)	4 (2.5)	0.003
NT-proBNP increased	9 (5.5)	25 (15.3)	0.006

* P values were calculated with the use of Fisher's exact test.
† A list of serious adverse events is shown in Table S5.
‡ Shown are the most frequently occurring adverse events occurring in more than 10% of patients in either group in the safety population, which comprised all patients who underwent randomization and received at least one dose of treprostinil or placebo.

with a lower risk of clinical worsening than that with placebo, a reduction in NT-proBNP levels, and fewer exacerbations of underlying lung disease.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

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