Efficacy of Inhaled Treprostinil on Multiple Disease Progression Events in Patients with Pulmonary Hypertension due to Parenchymal Lung Disease in the INCREASE Trial

Steven D. Nathan¹, Victor F. Tapson², Jean Elwing³, Franz Rischard⁴, Jinesh Mehta⁵, Shelley Shapiro⁶,⁷, Eric Shen⁸, Chunqin Deng⁸, Peter Smith⁸, and Aaron Waxman⁹

¹Advanced Lung Disease and Lung Transplant Program, Inova Fairfax Hospital, Falls Church, Virginia; ²Department of Medicine, Cedars-Sinai Medical Center, Los Angeles, California; ³Division of Pulmonary and Critical Care Medicine, Department of Medicine, University of Arizona, Tucson, Arizona; ⁴Pulmonary Medicine, Cleveland Clinic, Cleveland, Ohio; ⁵Cardiology Section, University of California Los Angeles David Geffen School of Medicine, Los Angeles, California; ⁶Division of Pulmonary Critical Care, VA Greater Los Angeles Healthcare System; ⁷United Therapeutics Corporation, Research Triangle Park, North Carolina; and ⁸Pulmonary and Critical Care Medicine, Brigham and Women’s Hospital, Boston, Massachusetts

ORCID IDs: 0000-0002-6270-1617 (S.D.N.); 0000-0001-9708-1457 (V.F.T.); 0000-0002-6199-1707 (J.E.); 0000-0002-6861-8304 (F.R.); 0000-0001-5621-6570 (E.S.); 0000-0002-5641-4101 (C.D.); 0000-0002-2051-7774 (P.S.); 0000-0001-7797-0361 (A.W.).

Abstract

Rationale: The INCREASE study of inhaled treprostinil met its primary endpoint of change in 6-minute-walk distance at Week 16. In addition, there were significantly fewer clinical worsening events in patients receiving inhaled treprostinil. However, the incidence of multiple events in the same patient is unknown.

Objectives: This post hoc analysis evaluated the effect of continued treatment with inhaled treprostinil on the frequency and impact of multiple disease progression events.

Methods: Patients enrolled in INCREASE were analyzed for disease progression events, defined as at least 15% decline in 6-minute-walk distance, exacerbation of underlying lung disease, cardiopulmonary hospitalization, lung transplantation, at least 10% decline in forced vital capacity, or death during the duration of the 16-week study.

Measurements and Main Results: In total, 147 disease progression events occurred in the inhaled treprostinil group (89/163 patients, 55%) compared with 215 events (109/163 patients, 67%) in the placebo group (P=0.018). There was a lower incidence of each disease progression component in the inhaled treprostinil group: 6-minute-walk distance decline (45 vs. 64 events), lung disease exacerbation (48 vs. 72 events), FVC decline (19 vs. 33), cardiopulmonary hospitalization (23 vs. 33 events), and death (10 vs. 12). Fewer patients receiving inhaled treprostinil had multiple progression events compared with those receiving the placebo (35 vs. 58, 22% vs. 36%; P=0.005).

Conclusions: Patients who received inhaled treprostinil were significantly less likely to experience further disease progression events after an initial event compared with patients receiving placebo. These results support the continuation of inhaled treprostinil despite the occurrence of disease progression in clinical practice.

Keywords: pulmonary hypertension; interstitial lung disease; prostacyclin
Pulmonary hypertension (PH) frequently complicates the course of patients with various forms of interstitial lung disease (ILD) (1). Patients with ILD complicated by PH (PH-ILD) have worse outcomes, including worsened functional status, increased supplemental oxygen requirements, increased healthcare resource usage, and increased mortality (2, 3). While there are a number of treatment options for ILD, including immunosuppressive therapy for those with an inflammatory component and antifibrotic therapy for those with a fibrotic predisposition, until recently there were no approved treatment options available for patients with PH-ILD (4, 5).

Trehperosinil is a stable analog of prostacyclin that promotes direct vasodilation of pulmonary and systemic arterial vascular beds and inhibits platelet aggregation (6). The inhaled formulation of treprostinil was initially approved in the United States based on a study demonstrating an improved exercise capacity after 12 weeks of therapy in group 1 PH (7). More recently, results from the INCREASE study were published. This was a 16-week, phase III, multicenter, randomized, double-blind, placebo-controlled study evaluating inhaled treprostinil in patients with PH-ILD (8). The study met its primary endpoint of change in the 6-minute-walk distance (6MWD) at peak exposure at Week 16, and inhaled treprostinil has now been approved in the United States as the first agent for the treatment of PH-ILD (9).

Notably, a number of secondary endpoints were met, including significantly fewer clinical worsening events in patients receiving inhaled treprostinil compared with placebo (hazard ratio [HR], 0.61; log-rank test, \( P = 0.04 \)). Clinical worsening in the INCREASE study was defined as time to the first of the following events: a 15% reduction in the 6MWD, cardiopulmonary hospitalization, lung transplantation, or death. Once patients met the first of these endpoints, then subsequent clinical worsening episodes were disregarded for further analysis. Therefore, the incidence of multiple events in the same patient is unknown, but it is of clinical interest given the propensity for further progression in most ILDs. Two of the four components of the composite endpoint can be followed by further worsening events; specifically, after experiencing a 15% reduction in their 6MWD or being hospitalized, patients are still at risk of further disease progression events. Of the other two endpoints, not only is death a terminating event, but lung transplant is “terminating” as well with regards to any worsening being attributable to the patient’s primary disease.

We hypothesize that inhaled treprostinil has continued clinical benefits compared with placebo in spite of patients experiencing a disease progression event. To test our hypothesis, we performed a post hoc analysis evaluating the effect of continued treatment with inhaled treprostinil in comparison with placebo on the frequency and impact of multiple disease progression events in the INCREASE study to provide a holistic view of treatment response. Preliminary results from this analysis have been previously reported in the form of an abstract (10).

Methods

INCREASE was a multicenter, randomized, double-blind, placebo-controlled trial of inhaled treprostinil in patients with PH-ILD. The steering committee in collaboration with the study sponsor (United Therapeutics Corporation) designed the study and oversaw its conduct. Detailed study procedures and results have been described previously (8). The INCREASE study (NCT02630316) was registered with ClinicalTrials.gov.

An important prespecified endpoint of the INCREASE study was time to clinical worsening defined as time to the first of the following four possible events: at least 15% decline in 6MWD, cardiopulmonary hospitalization, lung transplantation, or death during the study. A 10% decline in the FVC and exacerbations of underlying lung disease were collected as safety endpoints and were not included as part of the prespecified composite of clinical worsening. Pulmonary function testing (PFT) was performed locally at each clinical study site.
Clinical study sites were thoroughly evaluated for clinical trial experience. All study procedures, including PFT, were conducted under current good clinical practices. Acute exacerbations were determined by each site’s principal investigator and were defined by the clinical study protocol based on the most recent definition by Collard and colleagues as “acute, clinically significant respiratory deterioration characterized by new widespread alveolar abnormality” (11). The clinical trial protocol section on exacerbations can be found in the online supplement. Given the prognostic importance of FVC declines and exacerbations in the clinical course of ILD, we expanded the definition of disease progression to include these two events in this analysis (12–16). Therefore, this post hoc analysis sought to assess all disease progression events in patients who received inhaled treprostinil versus placebo after an initial disease progression event.

Statistical Analysis
The analyses conducted for this manuscript were post hoc and exploratory. The methodology used was based on a similar analysis of patients receiving pirfenidone (17). All assessments were summarized by descriptive statistics, as appropriate. All patients enrolled in the INCREASE study (n = 326) were included in this analysis. Disease progression was defined as either 15% or more decline in 6MWD, 10% or more decline in FVC, acute exacerbation, cardiopulmonary hospitalization, lung transplantation, or death. Events that occurred on the same day were assigned to the most serious event as ordered above. Proportions were compared via chi-square tests. Disease progression event rates were compared using negative binomial regression with the number of events as the dependent variable and log of time on treatment as an offset.

A confirmatory sensitivity analysis was conducted using only the four components of the original prespecified composite endpoint clinical worsening (≥15% decline in 6MWD, cardiopulmonary hospitalization, lung transplantation, or death). This sensitivity analysis was performed as specified above for the primary analysis. A second confirmatory sensitivity analysis based on the maximum number of events in a single patient calculated the average HR and its 95% confidence interval (CI) weighted across individual events. Because few patients had five or more disease progression events, a second sensitivity analysis that considered up to four events was also performed. Time to event endpoints was assessed with Kaplan-Meier curves and associated log-rank tests. Patients with zero events were censored in the first event Kaplan-Meier curves. Patients with zero or one events were censored in the second event Kaplan-Meier curves. Cox regression was used to calculate HRs and CIs. P values of 0.05 or less were considered significant, and no adjustments were made for multiplicity.

Results
A total of 326 patients (inhaled treprostinil, n = 163; placebo, n = 163) who were enrolled in the INCREASE study were included in this analysis. The mean age of the patients was 66.5 years, 46.9% were female, and 44.8% were diagnosed with idiopathic interstitial pneumonia (IIP), which was the most common disease etiology. Baseline characteristics were similar between the two groups as previously reported (8). Table 1 summarizes the baseline characteristics for patients with one and more than one disease progression event.

A total of 147 disease progression events occurred in the inhaled treprostinil group (89 patients, 55%) compared with 215 events (109 patients, 67%) in the placebo group (rate ratio, 0.69, 95% CI, 0.51–0.94; P = 0.018). The total number of each type of event is shown in Table 2.

After the first disease progression event, there were 35 subjects in the inhaled treprostinil group who had at least one additional event versus 58 subjects in the placebo arm (P = 0.005). Figure 1 is a waterfall plot depicting the incidence and sequence of multiple events over 16 weeks in patients receiving inhaled treprostinil (Figure 1A) and placebo (Figure 1B) sorted by increasing event frequency. Among patients with multiple disease progression events, the most frequent events were 6MWD decline (inhaled treprostinil vs. placebo, 24 vs. 45 events), exacerbation of lung disease (inhaled treprostinil vs. placebo, 37 vs. 57 events), decline in FVC (inhaled treprostinil vs. placebo, 9 vs. 20 events), and cardiopulmonary hospitalization (inhaled treprostinil vs. placebo, 17 vs. 29 events).

Death (depicted as light green in Figure 1), occurring after at least 1 disease progression event occurred less frequently in the inhaled treprostinil group (5 patients out of 163, 3%) than in the placebo group (12 patients out of 163, 7%), but this difference did not reach significance (P = 0.081). Patients who received treatment with inhaled treprostinil had a significantly lower risk of a single disease progression event (HR, 0.71; 95% CI, 0.54–0.94; P = 0.019) as well as a significantly lower risk of experiencing a second disease progression event compared with those who received placebo (HR, 0.53; 95% CI, 0.35–0.81; P = 0.003) (Figure 2). Inhaled treprostinil was also associated with significantly delayed time to first event and second event (log-rank P = 0.041, log-rank P = 0.009).

The sensitivity analyses confirmed these results. In the first sensitivity analysis employing the four original components of disease progression (≥15% decline in 6MWD, cardiopulmonary hospitalization, lung transplantation, or death), there were fewer events in the inhaled treprostinil group compared with the placebo group. The rate ratio was numerically similar to the primary analysis but did not reach significance (rate ratio, 0.70; 95% CI, 0.47–1.04; P = 0.081). Significantly fewer patients in the inhaled treprostinil group had multiple events (29 patients out of 163, 18%, with >1 event) than in the placebo group (50 patients out of 163, 31% with >1 event; P = 0.007) (see Figure E1 in the online supplement). In the second sensitivity analysis, patients who received inhaled treprostinil had a HR of 0.69 (95% CI, 0.53–0.89, P = 0.004) relative to placebo for up to six disease progression events (the maximum experienced by a single patient) and a HR of 0.69 (95% CI, 0.53–0.89; P = 0.004) for up to four events.

Subgroup Analyses
IIPs. Of the 146 patients with an IIP, there were a total of 54 disease progression events in the inhaled treprostinil group compared with 103 in the placebo arm. There were 11/65 subjects (17%) in the inhaled treprostinil group who had more than one disease progression event versus 26/81 (32%) in the placebo group (P = 0.036). These disease progression events were constituted by 6MWD decline (inhaled treprostinil vs. placebo, 7 vs. 20 events); cardiopulmonary hospitalization (inhaled treprostinil versus...
placebo; 6 vs. 15 events); exacerbation of lung disease (inhaled treprostinil versus placebo; 10 vs. 24 events); FVC decline (inhaled treprostinil versus placebo; 4 vs. 10 events); and death (inhaled treprostinil vs. placebo; 2 vs. 5 events, \( P = 0.384 \)). The waterfall plot in Figure 3A illustrates the incidence and sequence of multiple events in the IIP patients over 16 weeks in patients receiving placebo and inhaled treprostinil sorted by increasing event frequency.

**Table 2.** Number of Events by Treatment Arm

| Event                        | Total Number of Events | Among Subjects Who Had 1 Event | Among Subjects Who Had >1 Event |
|------------------------------|------------------------|-------------------------------|--------------------------------|
|                              | Inhaled Treprostinil   | Placebo                       | Inhaled Treprostinil           | Placebo |
|                              | \((n = 89)\)           | \((n = 109)\)                 | \((n = 54)\)                   | \((n = 51)\) |
|                              |                        |                               |                                |          |
| Decline in 6MWD \(>15\)%     | 45                     | 64                            | 21                             | 19       |
| Exacerbation                 | 48                     | 72                            | 11                             | 15       |
| Decline in FVC \(>10\)%      | 19                     | 33                            | 10                             | 13       |
| Cardiopulmonary hospitalization | 23                   | 33                            | 6                              | 4        |
| Lung transplantation          | 2                      | 1                             | 1                              | 0        |
| Death                        | 10                     | 12                            | 5                              | 0        |
| Total                        | 147                    | 215                           | 54                             | 51       |

**Definition of abbreviations:** 6MWD = 6-minute-walk distance.

**Idiopathic pulmonary fibrosis.** Of the 92 patients with idiopathic pulmonary fibrosis (IPF), there were a total of 37 disease progression events in the inhaled treprostinil group compared with 65 in the placebo group. There were 7/37 subjects (19%) in the inhaled treprostinil group who had more than one event versus 16/55 (29%) in the placebo group (\( P = 0.269 \)). These disease progression events were constituted by 6MWD decline (inhaled treprostinil vs. placebo, 4 vs. 10 events); cardiopulmonary hospitalization (inhaled treprostinil vs. placebo, 4 vs. 9 events); exacerbation of lung disease (inhaled treprostinil vs. placebo, 9 vs. 15 events); FVC decline (inhaled treprostinil vs. placebo, 3 vs. 7 events); and death (inhaled treprostinil vs. placebo, 1 vs. 4 events; \( P = 0.343 \)). The waterfall plot in Figure 3B illustrates the incidence and sequence of multiple events in the patients with IPF over 16 weeks in patients receiving placebo and inhaled treprostinil, sorted by increasing event frequency.

**Table 1.** Baseline Characteristics for Patients with One Event and More Than One Event

| Event                        | \(1\) Event \((n = 198)\) | \(>1\) Event \((n = 198)\) |
|------------------------------|---------------------------|---------------------------|
|                              | Inhaled Treprostinil      | Placebo                   | Inhaled Treprostinil           | Placebo |
|                              | \((n = 54)\)              | \((n = 51)\)              | \((n = 35)\)                   | \((n = 58)\) |
| Female, \(n (%)\)           | 28 (52%)                  | 19 (37%)                  | 18 (51%)                      | 28 (48%) |
| Age, yr, mean (SD)          | 64 (14)                   | 68 (11)                   | 66 (11)                       | 67 (11)  |
| White, \(n (%)\)            | 39 (72%)                  | 42 (82%)                  | 24 (69%)                      | 42 (72%) |
| BMI, kg/m², mean (SD)       | 30.2 (7.4)                | 28.9 (6.3)                | 29.7 (5.7)                    | 27.9 (5.4) |
| Years since PH-ILD diagnosis, mean (SD) | 0.5 (0.7)                  | 0.3 (0.3)                  | 0.6 (1.2)                     | 0.7 (1.3) |
| Disease etiology, \(n (%)\) |                          |                           |                                |          |
| IIP                          |                          |                           |                                |          |
| IPF only                     | 16 (30%)                  | 20 (39%)                  | 7 (20%)                       | 18 (28%) |
| CPFE                         | 11 (20%)                  | 7 (14%)                   | 12 (34%)                      | 17 (29%) |
| CTD-ILD                      | 16 (30%)                  | 11 (22%)                  | 6 (17%)                       | 13 (22%) |
| 6-min-walk distance, m, mean (SD) | 247 (99)                  | 273 (89)                  | 211 (80)                      | 235 (92) |
| NT-proBNP, pg/ml, mean (SD)  | 1,981 (3,349)             | 931 (1,257)               | 2,431 (2,985)                 | 3,160 (4,382) |
| Hemodynamics, mean (SD)      |                          |                           |                                |          |
| PAPm, mm Hg                  | 38.4 (9.8)                | 35.0 (7.9)                | 38.8 (9.7)                    | 37.1 (8.9) |
| PCWP, mm Hg                  | 10.6 (3.4)                | 9.8 (3.1)                 | 10.4 (3.7)                    | 9.9 (3.8) |
| PVR, Wood units              | 6.5 (3.2)                 | 5.6 (2.2)                 | 6.7 (2.5)                     | 6.6 (3.3) |
| Lung function tests, mean (SD) |                        |                           |                                |          |
| TLC % predicted              | 62 (16)                   | 65 (21)                   | 62 (18)                       | 65 (16)  |
| FVC % predicted              | 60 (19)                   | 63 (22)                   | 61 (19)                       | 63 (20)  |
| FEV1 % predicted             | 61 (19)                   | 65 (21)                   | 61 (20)                       | 65 (20)  |
| DLCO % predicted             | 30 (12)                   | 29 (10)                   | 29 (13)                       | 25 (13)  |

**Definition of abbreviations:** BMI = body mass index; CPFE = combined pulmonary fibrosis and emphysema; CTD-ILD = connective tissue disease–associated interstitial lung disease; IIP = idiopathic interstitial pneumonia; IPF = idiopathic pulmonary fibrosis; NT-proBNP = N-terminal pro–brain natriuretic peptide; PAPm = mean pulmonary arterial pressure; PCWP = pulmonary capillary wedge pressure; PH-ILD = interstitial lung disease complicated by pulmonary hypertension; PVR = pulmonary vascular resistance.
Figure 1. Incidence and sequence of multiple disease progression events up to 16 weeks in patients randomized to (A) inhaled treprostinil versus (B) placebo who had more than one event. Patients were sorted on the x-axis by increasing number of total events, which are shown on the y-axis in the order of occurrence for each patient. 6MWD = 6-minute-walk distance.
Combined pulmonary fibrosis and emphysema. Of the 82 patients with combined pulmonary fibrosis and emphysema (CPFE), there were a total of 41 disease progression events in the inhaled treprostinil group compared with 50 in the placebo group. There were 12/42 subjects (29%) in the inhaled treprostinil group who had more than one event versus 17/40 (43%) in the placebo group ($P = 0.187$). These disease progression events were constituted by 6MWD decline (inhaled treprostinil vs. placebo, 6 vs. 9 events); cardiopulmonary hospitalization (inhaled treprostinil vs. placebo, 7 vs. 7 events); exacerbation of lung disease (inhaled treprostinil vs. placebo, 12 vs. 18 events); FVC decline (inhaled treprostinil vs. placebo, 2 vs. 4 events); and death (inhaled treprostinil vs. placebo, 3 vs. 5 events; $P = 0.414$). Figure 3C illustrates the incidence and sequence of multiple events in the patients with CPFE over 16 weeks in patients receiving placebo and inhaled treprostinil sorted by increasing event frequency.

Connective tissue disease–associated ILD. Of the 72 patients with a connective tissue disease–associated ILD (CTD-ILD), there were a total of 31 disease progression events in the inhaled treprostinil group compared with 52 in the placebo group. There were 6/40 subjects (15%) in the inhaled treprostinil group who had more than one event versus 13/32 (41%) in the placebo group ($P = 0.014$). These disease progression events were constituted by 6MWD decline (inhaled treprostinil vs. placebo, 4 vs. 16 events); cardiopulmonary hospitalization (inhaled treprostinil vs. placebo, 2 vs. 7 events); exacerbation of lung disease (inhaled treprostinil vs. placebo, 7 vs. 12 events); FVC decline (inhaled treprostinil vs. placebo, 2 vs. 3 events); and death (inhaled treprostinil vs. placebo, 0 vs. 2 events; $P = 0.109$). Figure 3D illustrates the incidence and sequence of multiple events in the patients with CTD-ILD over 16 weeks in patients receiving placebo and inhaled treprostinil, sorted by increasing event frequency.

Discussion

The INCREASE study comparing inhaled treprostinil to placebo in patients with PH-ILD met its primary endpoint of change in the 6MWD over 16 weeks (8). An important supportive secondary endpoint was time to clinical worsening, which the study protocol defined as the first of four possible events: a 15% decrease in the 6MWD, cardiopulmonary hospitalization, lung transplantation, or death. There were very few patients who met this endpoint through the last two components; specifically, there were only two patients who underwent lung transplantation before any of the other endpoints were met (both in the treatment arm), whereas four patients in each group had death as the first event. The majority of patients met the time to clinical worsening endpoint through a 15% decrease in their 6MWD or hospitalization and therefore remained at risk for further worsening events. Safety endpoints captured during the trial included both acute...


**Figure 3.** Incidence and sequence of multiple disease progression events up to 16 weeks by treatment arm for patients with (A) idiopathic interstitial pneumonias, including idiopathic pulmonary fibrosis (IIP); (B) idiopathic pulmonary fibrosis only (IPF); (C) combined pulmonary fibrosis and emphysema (CPFE); and (D) connective tissue disease (CTD). 6MWD = 6-minute-walk distance.
exacerbations of the underlying lung disease and decline in the FVC. Although these could have been regarded as clinical worsening, they were designated as safety endpoints as it was unknown whether inhaled treprostinil might have deleterious effects in patients with intrinsic lung disease. In the current analysis, we therefore included FVC decline and lung disease exacerbations in our expanded definition of disease progression. Such an analysis provides important information on the benefits of

Figure 3. (Continued).

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continuation of inhaled treprostinil for patients who have had a disease progression event.

In this current analysis, we demonstrate that significantly fewer patients who were treated with inhaled treprostinil had a disease progression event. Furthermore, analysis of subsequent clinical events after the first occurrence demonstrates ongoing benefit from the continuation of inhaled treprostinil. Specifically, only 39% (35 of 89) of patients on inhaled treprostinil who experienced one event had one or more subsequent events during the course of the 16-week study versus 53% (58 of 109) in the placebo group. Not only were the patients receiving inhaled treprostinil at reduced risk of disease progression, but time to first event as well as time to second event were delayed in comparison to the patients receiving placebo. Our subgroup analyses demonstrated that this significantly reduced risk of multiple disease progression events was evident in most of the major disease subgroups, including patients with any IIP and CTD-ILD, but not CPFE or IPF alone.

The value of this comprehensive analysis of all disease progression events is that it provides a global overview of the benefit of inhaled treprostinil therapy over 16 weeks. Although the risk of a first clinical worsening event being reduced in PH-ILD using inhaled treprostinil has previously been reported, this analysis further builds on this by providing insight on subsequent disease progression occurring at any time during the INCREASE trial (8). It is also notable that among the 22 total deaths in both active and placebo arms, 11 occurred after a cardiopulmonary hospitalization (3 inhaled treprostinil and 8 placebo) and 8 occurred after an acute exacerbation (2 inhaled treprostinil and 6 placebo). This highlights the prognostic significance of both such events (11, 17, 18). Whether patients with ILD who are hospitalized for a cardiopulmonary cause or suffer an acute exacerbation are at higher risk for having underlying PH, and whether these events should prompt an evaluation for PH, is a subject for future research.

Our current umbrella of six possible clinical worsening events differs from that of the primary analysis, as in addition to a 15% reduction in the 6MWT, respiratory hospitalizations, lung transplantation, or death, we also included acute exacerbations of the underlying lung disease and a 10% decline in the FVC as clinically meaningful worsening events. However, the robustness of our findings is supported by our sensitivity analysis using the four prespecified endpoints only. This type of approach holds lessons for future PH-ILD clinical trials; specifically, including all clinically relevant endpoints not only enables a comprehensive overview of the intervention’s benefits but might also enable the capture of sufficient events to demonstrate a difference over a relatively short period of time. The fact that the placebo group had so many clinical worsening events over the relatively short period of 16 weeks underscores the high-risk nature of patients with PH-ILD, a group that is in dire need of further studies to investigate therapeutic interventions.

There are limitations to this study. First, this was a post hoc analysis and we did not incorporate events that we had a priori designated as safety endpoints in our composite of disease progression events. In addition, acute exacerbations were determined by the principal investigator at each site and were not centrally adjudicated. Therefore, we cannot validate that these were true acute exacerbations based on the formal definition, but they undoubtedly reflected some measure of worsening of clinical status (15). Follow-up PFT was only measured twice, at the Week 8 and Week 16 study visits, limiting the ability to confirm the FVC component of disease progression. Lastly, this analysis was limited by the short follow-up time of 16 weeks and the smaller sample size of patients who experienced multiple events.

Conclusions

In the INCREASE study, patients who received inhaled treprostinil were significantly less likely to experience further disease progression events when compared with patients on placebo. In clinical practice, some patients and physicians may consider changing or discontinuing therapies when there are signs of progression of PH-ILD. Results from this novel analysis support the continuation of inhaled treprostinil despite evidence of clinical worsening and are consistent with the significant results for the study’s primary endpoint previously reported.

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