Inhaled treprostinil in patients with pulmonary hypertension associated with interstitial lung disease with less severe haemodynamics: a post hoc analysis of the INCREASE study

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ABSTRACT

Background Inhaled treprostinil (iTre) is the only treatment approved for pulmonary hypertension due to interstitial lung disease (PH-ILD) to improve exercise capacity. This post hoc analysis evaluated clinical worsening and PH-ILD exacerbations from the 16-week INCREASE study and change in 6-minute walking distance (6MWD) in the INCREASE open-label extension (OLE) in patients with less severe haemodynamics.

Methods Patients were stratified by baseline pulmonary vascular resistance (PVR) of <4 Wood units (WU) versus ≥4 WU and <5 WU versus ≥5 WU. Exacerbations of underlying lung disease, clinical worsening and change in N-terminal prohormone of brain natriuretic peptide (NT-proBNP) in INCREASE were evaluated. For the OLE, patients previously assigned to placebo were considered to have a 16-week treatment delay. 6MWD and clinical events in the OLE were evaluated by PVR subgroup.

Results Of the 326 patients enrolled in INCREASE, patients with less severe haemodynamics receiving iTre had fewer exacerbations of underlying lung disease and clinical worsening events. This was supported by the Bayesian analysis of the risk of disease progression (HR<1), and significant decreases in NT-proBNP levels. In the OLE, patients without a treatment delay had improved exercise capacity after 1-year compared with those with a 16-week treatment delay (22.1 m vs −10.3 m). Patients with a PVR of ≤5 WU without a treatment delay had a change of 5.5 m compared with −8.2 m for those with a treatment delay. Patients without a treatment delay had a prolonged time to hospitalisation, lung disease exacerbation and death.

Conclusion Treatment with iTre led to consistent benefits in clinical outcomes in patients with PH-ILD and less severe haemodynamics. Earlier treatment in less severe PH-ILD may lead to better exercise capacity long-term, however, the subgroup analyses in this post hoc study were underpowered and confirmation of these findings is needed.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Inhaled treprostinil, a prostacyclin mimetic, was approved for the treatment of pulmonary hypertension due to interstitial lung disease (PH-ILD) in the US based on the 6-minute walk distance (6MWD) improvement demonstrated in INCREASE, a 16-week, randomised controlled trial (RCT). The effects of inhaled treprostinil in patients with less severe haemodynamics have been a topic of interest in the PH-ILD community.

WHAT THIS STUDY ADDS

⇒ This post hoc analysis of the INCREASE RCT suggests that there could be benefits of treatment with inhaled treprostinil in patients with less severe haemodynamics on clinical outcomes apart from 6MWD. Additionally, analyses from the open-label extension study found that after a 16-week treatment delay, patients with less severe pulmonary vascular disease may not achieve the same improvements as those who had no delay in treatment. Together, these findings suggest the importance of screening, diagnosis and treatment of patients with PH-ILD regardless of their level of haemodynamic impairment.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Earlier treatment in patients with PH-ILD and mild haemodynamic impairment may result in improvements in multiple clinically relevant outcomes and may prevent or delay disease progression and other untoward longer-term sequelae that these patients might otherwise experience. As the post hoc subgroup analyses in this study were underpowered, further research is needed to confirm the benefit of treatment in patients with PH-ILD and mild haemodynamic impairment.
INTRODUCTION
Pulmonary hypertension (PH) is defined by a mean pulmonary arterial pressure (mPAP) ≥20 mm Hg, pulmonary capillary wedge pressure (PCWP) ≤15 mm Hg and pulmonary vascular resistance (PVR) of ≥2 Wood units (WU). The sixth World Symposium on Pulmonary Hypertension classified pre-capillary PH due to lung disease and/or hypoxia as Group 3 PH. This classification includes PH due to interstitial lung disease (PH-ILD), which encompasses a heterogeneous group of parenchymal lung diseases classified by scarring or fibrosis of the lung parenchyma and diffusion impairment and includes idiopathic pulmonary fibrosis, interstitial pneumonia, connective tissue disease-associated ILD, chronic hypersensitivity pneumonia and occupational lung disease. The incidence of PH in patients with ILD varies but has been reported to be as high as 86% at the time of transplant.

Inhaled treprostinil (available as Tyvaso nebulised solution and Tyvaso dry powder inhaler), a prostacyclin mimetic, was granted approval by the US Food and Drug Administration for use in patients with PH-ILD (previously approved for pulmonary arterial hypertension) to improve exercise ability, based on the outcomes of INCREASE, which was a 16-week, randomised controlled trial (RCT). Inclusion criteria for this trial was based on the 2015 European Respiratory Society/European Society of Cardiology (ERS/ESC) definition for PH and included patients with mPAP ≥25 mm Hg, PVR of >3 WU and PCWP of ≤15 mm Hg. The trial met its primary endpoint of change in 6-minute walking distance (6MWD) as well as numerous secondary endpoints, including time to clinical worsening and change in N-terminal prohormone of brain natriuretic peptide (NT-proBNP). In a prespecified subgroup analysis of patients with a baseline PVR of 3–4 WU, inhaled treprostinil did not lead to statistically significant improvements in 6MWD compared with placebo. The INCREASE study was not powered for detecting a 6MWD improvement in this subgroup, and the effects of inhaled treprostinil on other clinical outcomes in patients with less severe haemodynamics have not been previously reported, which would be of interest in the PH-ILD community.

In this post hoc analysis of the INCREASE study, our primary objective was to evaluate the effect of inhaled treprostinil on clinical outcomes such as NT-proBNP in patients with less severe haemodynamics from the randomised placebo-controlled phase. Our secondary objective was to explore the effect of a 16-week delay in treatment on 6MWD and clinical outcome events in patients with less severe haemodynamics in the INCREASE open-label extension (OLE).

METHODS
The INCREASE study was a 16-week randomised, double-blind, placebo-controlled, trial that evaluated the safety and efficacy of inhaled treprostinil in patients with PH-ILD (ClinicalTrials.gov ID NCT02630316). Detailed study procedures and results have been described previously. Briefly, the population included patients ≥18 years with a diagnosis of ILD based on evidence of diffuse parenchymal lung disease on CT completed within 6 months before randomisation. Diagnosis of PH by right heart catheterisation using the 2015 ERS/ESC definition (PVR>3 WU, PCWP≤15 mm Hg, mPAP≥25 mm Hg) within 1 year of randomisation was required.

An OLE of the INCREASE trial was performed to evaluate the safety and efficacy of long-term treatment with inhaled treprostinil. Study procedures and results were recently published. All patients in the OLE received inhaled treprostinil. Thus, for this post hoc analysis, patients who were previously assigned to the placebo group in the randomised portion of the study were considered to have a 16-week treatment delay.

Patient and public involvement statement
Patients were not involved in the development of study design or recruitment of participants.

INCREASE RCT post hoc analysis
The first portion of the post hoc analysis analysed change from baseline in NT-proBNP, exacerbation of underlying lung disease, clinical worsening events and disease progression from the initial 16-week INCREASE RCT. Clinical worsening was defined as the first occurrence of any one of the following: hospitalisation due to a cardiopulmonary indication, >15% 6MWD decline from baseline, lung transplantation or death. Exacerbation of underlying disease, as reported by investigators as a safety endpoint, was defined as an acute, clinically significant respiratory deterioration, characterised by evidence of new widespread alveolar abnormalities. Lastly, we defined the composite endpoint of disease progression as the first occurrence of either clinical worsening or exacerbation. It should be noted that exacerbations were a safety endpoint in the INCREASE study but given the findings of the study and the clinical relevance of exacerbations in patients with ILD, they were included in this ‘pragmatic’ composite endpoint to provide a more holistic view of the effects of inhaled treprostinil.

Patients were stratified by baseline PVR; patients with a PVR≤4 WU were compared with those with a PVR≥4 WU to reflect the same threshold as the original subgroup analysis from the INCREASE study. Additionally, the 2022 ESC/ERS guidelines for PH define ‘severe’ PH in Group 3 patients as PVR≥5 WU so this was selected as another threshold for PH severity of clinical interest to physicians (PVR≥5 WU vs ≤5 WU) for this post hoc analysis.

Bayesian analyses of time to disease progression were also performed stratifying by the same PVR thresholds to supplement the conventional frequentist analysis of disease progression and to offer a different approach to interpret the data for the composite endpoint of disease progression. In a Bayesian framework, prior beliefs
or knowledge about the possible range of treatment effect values are combined with observed data, and this combined information is represented as a posterior probability distribution. Four prior distributions were specified to represent different levels of scepticism regarding the efficacy of inhaled treprostinil: non-informative, optimistic, neutral and pessimistic. A non-informative prior deems all possible log HR values as equally plausible, leading to a posterior inference that is primarily driven by the trial data.

Consistent with the frequentist conventional null hypothesis of ‘no benefit’ (HR=1), the probability of treatment benefit (HR<1) and the probability of clinically important risk (HR<0.8) were estimated for time to disease progression. Additionally, Bayesian analyses of the time to the first clinical worsening event and time to exacerbation are presented in online supplemental materials. The proportional hazards regression procedure in SAS was employed to conduct the Bayesian survival analysis. SAS statistical software, V.9.4 (SAS Institute) was used for all analyses.

**INCREASE OLE post hoc analysis**

Using the INCREASE OLE data, patients previously assigned to the placebo group in the RCT were considered to have a 16-week treatment delay to elucidate the impact of delayed treatment on 6MWD after 1 year. Subgroups analysed include all patients enrolled in the OLE stratified by baseline PVR in the same manner as above. A similar analysis was performed with stratification by baseline mPAP of 35 mm Hg, as this was the 2015 ERS/ESC guideline definition of severe PH-ILD. Assessments were conducted at Week 4, Week 12 and then every 12 weeks. Time to first cardiopulmonary hospitalisation, time to acute exacerbation and time to death were evaluated for patients assigned to placebo in the RCT (16-week delayed treatment) versus patients assigned to inhaled treprostinil in the RCT (earlier treatment).

In the OLE analysis, Week 0 was defined as the start of inhaled treprostinil therapy. For patients previously assigned to inhaled treprostinil in the 16-week INCREASE study, Week 0 is the start of the parent trial and for those assigned to the placebo group in the randomised 16-week INCREASE trial, Week 0 is the start of the OLE. Due to the different follow-up schedules between the prior treatment and placebo arms, the 1-year time point is Week 48 for patients who were formerly assigned to the placebo arm (treatment delay) and Week 52 for those formerly in the treatment arm.

**Statistics**

The analysis population included patients who completed the INCREASE trial and all patients who received ≥1 dose of inhaled treprostinil at any time during the OLE. Continuous variables were assessed with summary statistics, including mean and SD. Percentages were calculated for discrete variables. Statistical significance was assessed with χ² tests for clinical worsening and exacerbation of underlying lung disease (results in online supplemental materials). Bayesian survival analyses based on the HR for time to disease progression were conducted, adjusting for baseline 6MWD for subjects with baseline PVR<4 WU and ≤5 WU as described above. For post hoc Bayesian analyses for clinical worsening and lung disease exacerbations, the probability of posterior median HR with 95% credible interval was reported. NT-proBNP (pg/mL) at Week 16 was measured using least-square mean of ratio to baseline and the p value for treatment differences was assessed using a mixed model for repeated measures model under the assumption that missing data were missing at random. Cox proportional hazards (HRs with 95% CIs) and p values were completed for analyses of cardiopulmonary hospitalisation, time to acute exacerbation and death.

**RESULTS**

**Patient demographics**

A total of 326 patients were enrolled in the initial phase 3 INCREASE trial, 163 received inhaled treprostinil and 163 received a placebo. When stratified into groups by the PVR threshold of 4 WU, there were 66 patients with a PVR range between 3 and 4 WU (inhaled treprostinil, n=32; placebo, n=34) and 260 patients with PVR>4 WU (inhaled treprostinil, n=131; placebo, n=129). For the PVR threshold of 5 WU, there were 150 patients with a PVR range between >3 WU and ≤5 WU (inhaled treprostinil, n=69; placebo, n=81) and 176 patients with PVR>5 WU (inhaled treprostinil, n=94; placebo, n=82). A total of 242 of these patients were enrolled in the OLE and received at least one dose of inhaled treprostinil. Overall, at baseline, patients with less severe haemodynamics had a numerically higher body mass index (BMI), higher 6MWD, lower NT-proBNP and lower mPAP (see online supplemental tables S1 and S2).

**INCREASE RCT post hoc analysis**

Inhaled treprostinil treatment was associated with significant decreases in NT-proBNP compared with placebo in patients with less severe haemodynamics, both when stratifying by a PVR of 4 WU as well as 5 WU (see figure 1A–D).

In the subgroup of patients receiving inhaled treprostinil in the 16-week RCT with a baseline PVR<4 WU, 6/32 (18.8%) had an exacerbation of their underlying lung disease compared with 11/34 (32.4%) of those in the placebo group (HR 0.56 (95% CI 0.21 to 1.51); p=0.25; figure 2A). Similarly, fewer patients with a baseline PVR≥4 WU who received treatment with inhaled treprostinil experienced exacerbation of their underlying lung disease compared with those in the placebo group, 37/131 (28.2%) compared with 52/129 (40.3%), respectively (HR 0.68 (95% CI 0.44 to 1.03); p=0.07). Patients with a PVR<5 WU and ≥5 WU also had fewer exacerbations of underlying lung disease (figure 2B). For those with a PVR≤5 WU, 14/69 (20.3%) receiving
inhaled treprostinil versus 32/81 (39.5%) on placebo experienced an exacerbation (HR 0.43 (95% CI 0.23 to 0.81); p=0.01). When stratified by a PVR>5 WU, 29/94 (30.9%) patients receiving inhaled treprostinil versus 31/82 (37.8%) on placebo (HR 0.87 (95% CI 0.52 to 1.44); p=0.56) experienced an exacerbation, respectively.

Patients who received inhaled treprostinil in the 16-week RCT also had fewer clinical worsening events (online supplemental table S3). A total of 3/32 (9.4%) patients with a baseline PVR<4 WU in the inhaled treprostinil group experienced a clinical worsening event versus 8/34 (23.5%) patients in the placebo group (HR 0.37 (95% CI 0.10 to 1.41); p=0.15) (figure 2A); this was also true for patients with a baseline PVR of ≥4 WU (HR 0.65 (95% CI 0.41 to 1.01); p=0.06). A similar trend was seen when stratified by PVR≤5 WU: 13/69 (18.8%) patients receiving inhaled treprostinil experienced a clinical worsening event versus 20/83 (24.1%) patients on placebo (HR 0.67 (95% CI 0.33 to 1.35); p=0.26) (figure 2B); similarly for PVR>5 WU, significantly fewer patients on inhaled treprostinil experienced a clinical worsening event (HR 0.55 (95% CI 0.32 to 0.92); p=0.03). A similar trend was seen when patients were stratified by baseline mPAP of 35 mm Hg (online supplemental table S4), patients receiving inhaled treprostinil (mPAP<35 mm Hg: 23/74 (31.1%), HR 0.58, p=0.04; mPAP≥35 mm Hg: 36/89 (40.4%), HR 0.81, p=0.37) had fewer overall disease progression events (clinical worsening or lung disease exacerbations) compared with placebo (mPAP<35 mm Hg: 39/80 (48.8%); mPAP≥35 mm Hg: 40/83 (48.2%)).

The Bayesian analysis of the risk of disease progression with the four prior distributions is shown in figure 3. Detailed information on the posterior distributions of the HR with the associated 95% credible intervals is listed in table 1. In summary, for patients with a baseline PVR<4 WU, the posterior probability of an HR<1 for every prior was above 75% for all priors except the pessimistic prior, with the highest probability using the optimistic prior as expected. For patients with a PVR<5 WU, the posterior probability of an HR<1 for every prior was above 95% for all priors except the pessimistic prior. Furthermore, the posterior probability of an HR<0.8 for every prior was above 80% for all priors apart from the pessimistic prior. Details on the Bayesian analysis for clinical worsening and exacerbations can be found in online supplemental tables S5 and S6.

**INCREASE OLE post hoc analysis**

In the OLE study, after 1 year, patients with a 16-week treatment delay had a 6MWD change of −10.3 m compared with 22.1 m for those without a treatment delay (figure 4A). Patients with a baseline PVR<4 WU with a 16-week treatment delay had a 6MWD change at 1 year of 13 m compared with −12.2 m in those without a treatment delay (figure 4B). At the prespecified time points prior to the 1-year mark (Week 48 for patients formerly assigned to placebo and Week 52 for those formerly receiving
patients without a delay of treatment had a numerically smaller 6MWD decrease than those with a treatment delay. At Week 48, there were only four patients in the treatment arm where patients formerly received a placebo. Of note, these patients had changes in 6MWD from baseline of −46 m, −18 m, −10 m and +126 m; the one improvement of +126 m resulted in a positive mean change at the 1-year mark. Patients with a baseline PVR of ≥5 WU with a treatment delay had a change of −8.2 m compared with 5.5 m for those without a treatment delay (figure 4C). The OLE 6MWD analysis performed using a baseline mPAP of 35 mm Hg was similar to those with a baseline PVR≤5 WU (online supplemental figure S1).

Patients treated earlier generally had a numerically decreased risk of cardiopulmonary hospitalisation, lung disease exacerbation and death, though these were only statistically significant for the lung disease exacerbation outcome in patients with PVR≥4 WU and in those with PVR≤5 WU (online supplemental table S7).

**DISCUSSION**

Overall, our post hoc analyses from the RCT suggested clinical benefits of treatment with inhaled treprostinil in patients with less severe haemodynamics; post hoc analysis of the INCREASE OLE data also suggest that after a 16-week treatment delay, patients with less severe pulmonary vascular disease might not be able to achieve the

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<th>Posterior median HR (95% credible interval)</th>
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<th>Probability HR&lt;0.8</th>
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N/A, not applicable; PVR, pulmonary vascular resistance; WU, Wood units.
same improvements as those who have no delay in treatment.

In the INCREASE study, inhaled treprostinil was shown to improve exercise capacity in patients with PH-ILD. Secondary analyses performed on the INCREASE data have also shown other clinical benefits of inhaled treprostinil treatment, including improvement in forced vital capacity and fewer multiple disease progression events compared with placebo.

The primary analysis of the INCREASE study contributed to an active debate among PH providers on whether patients with less severe haemodynamic impairment may derive benefit from inhaled treprostinil and whether treatment with inhaled treprostinil should be delayed until patients develop more severe PH. Specifically, a subgroup analysis of the 6MWD, the primary endpoint of the INCREASE study, showed no difference between the treatment and placebo arms for patients with a baseline PVR<4 WU. Given the ancillary benefits apart from the primary endpoint, and the availability of the OLE extension data, we had the opportunity to perform a more comprehensive assessment of inhaled treprostinil in those with less severe haemodynamic impairment.

The objective of this post hoc analysis was to examine other common clinical markers of disease outcomes in PH-ILD, along with long-term 6MWD results for an extended period of time compared with the originally available 16-week data to see if there was any measurable difference when delaying treatment in patients with less severe haemodynamic impairment.

Patients who received treatment in the initial 16-week study experienced fewer exacerbations of their underlying lung disease and fewer clinical worsening events. While the results for exacerbations were only significant in the ≤5 WU subgroup and clinical worsening events were only significant for the >5 WU subgroup, the HRs were <1 for all subgroups analysed, including those with PVR<4 WU. The interpretation of significance or non-significance of our results should be made with caution given the small size of these subgroups. The CIs for these HRs were wide, which is likely attributable to the low number of patients per subgroup, especially in the PVR<4 WU subgroup (n=66). The Bayesian analyses confirm a strong trend toward benefit for the use of inhaled treprostinil in both the PVR<4 WU and ≤5 WU subgroups with regard to disease progression, with posterior probabilities of an HR<1 consistently above 75% for both PVR stratifications across all priors apart from the pessimistic prior.

Additionally, NT-proBNP levels, a marker of myocardial stress and a commonly used biomarker for PH clinical trials, were reduced in patients with less severe haemodynamics treated with inhaled treprostinil versus placebo in the 16-week RCT, suggesting an improvement in cardiac strain even among the subgroup of patients with a baseline PVR<4 WU. A previous study suggested that in patients with chronic lung disease, BNP may be a risk factor for death, independent of impaired lung function or hypoxaemia. Moreover, research has shown that Group 3 patients have worse right ventricular (RV) function than Group 1 patients. The exact mechanisms behind the underlying worse RV function in these patients are unknown, but it has been postulated to be related to non-haemodynamic insults that result in RV dysfunction disproportionate to PH severity and/or differences in sex hormones. Thus, our post hoc analysis further supports the earlier implementation of therapy in those with less severe PH as amelioration of RV stress and strain may translate to long-term benefits.

In the INCREASE OLE, patients with a delay in treatment and less severe haemodynamics (PVR<5 WU) seemed to not achieve the same gains in exercise capacity compared with those who had no delay in treatment, but 6MWD remained stable over 1 year with little evidence of deterioration. This suggests that treatment effects on exercise capacity for patients with less severe haemodynamic impairment may still be realised over time, though it is important to note that these post hoc analyses were underpowered and were not statistically significant.

Though ILD generally follows a steadily progressive course, for patients who also develop PH, a 16-week period could be clinically meaningful in the light of the median survival time of 1.5–2 years after diagnosis of PH. Therefore, it may be feasible for a 16-week treatment delay to have considerable downstream implications in the setting of PH with underlying ILD. Given this increased risk of mortality for patients with PH-ILD with any level of haemodynamic severity and the dismal prognosis expected in PH-ILD compared with other forms of PH, the apparent absence of an improvement in the 6MWD in the former placebo group during the OLE study with inhaled treprostinil is not completely unwarranted either.

In patients with a baseline PVR<4 WU, a slight deterioration in 6MWD was observed in both cohorts, although those who had no delay in treatment had a numerically smaller decrease than those with a treatment delay until the 1-year time point. These apparent paradoxical results, when compared with the prior analysis, are again likely due to small sample sizes in the PVR<4 WU group and a drop-off in the number of patients with analysable data over the course of the OLE. For example, for patients with a baseline PVR of <4 WU, 32 patients in the former inhaled treprostinil group rolled over to the OLE (no treatment delay) and 23 former placebo patients (16-week treatment delay). At the 1-year time point, there were 18 patients in the former inhaled treprostinil group versus 4 in the former placebo group, resulting in outcomes with large dispersions that are difficult to interpret.

All patients without a treatment delay (ie, assigned to inhaled treprostinil in the RCT) generally had a longer time to the first hospitalisation due to cardiopulmonary indication, longer time to first exacerbation of underlying lung disease and longer time to death compared with patients with a treatment delay (ie, assigned to placebo in the RCT). For the ≥4 WU subgroup’s time to...
the first hospitalisation, an opposite trend was seen with an HR of slightly >1. While only the time to first exacerbation of underlying lung disease for the ≥4 WU and ≤5 WU subgroups was significant, the risk reduction for the other clinical events supports a treatment benefit versus placebo, showing that patients without a treatment delay are less likely to be hospitalised due to a cardio-pulmonary event and less likely to have a lung disease exacerbation. Of note, data from the INCREASE OLE also showed a numerically but not significantly lower risk of cardiopulmonary hospitalisation in patients with a PVR<4 WU and PVR≥5 WU in patients without a treatment delay. Although these analyses were not designed to detect a treatment difference between these PVR groups, the results suggest that there may be treatment benefits in patients with less severe haemodynamics that were not reflected by the 6MWD results originally reported. These results support the need for additional prospective studies in patients with milder haemodynamics.

Registry data in patients with ILD support the notion that any degree of haemodynamic impairment in this patient population portends a poor outcome. In the Spanish Registry of PH in Respiratory Disease, patients with borderline PH (mPAP 23 mm Hg, PVR 3.5 WU) had similarly dismal survival as patients with moderate PH (mPAP 29 mm Hg, PVR 4.7 WU) and severe PH (mPAP 41 mm Hg, PVR 7.7 WU). In combination with data from our post hoc analyses, these results suggest that therapy to treat PH-ILD should not be delayed until patients are more haemodynamically compromised. This is also reflected in current practice guidelines from the ESC/ERS that state that inhaled treprostinil may be considered in patients with PH-ILD irrespective of PH severity.

Our post hoc analysis has several limitations. There were differences in baseline characteristics, such as BMI, exercise capacity and NT-proBNP, which could have confounded our results. Also, as a post hoc analysis, the study was not designed to compare the subgroups presented here. Additionally, this analysis is limited by the small sample size in certain subgroups, particularly in the PVR<4 group and at later time points in the OLE, which may account for the lack of statistical significance and conflicting results in some measures. As such, it is important to interpret any statistically significant or non-significant results with caution. Lastly, the OLE outcome measures were assessed at Week 52 for patients who were randomised to treatment in the RCT compared with Week 48 for placebo, and the extra 4 weeks of treatment may confound our results.

In summary, this post hoc analysis suggests that earlier treatment in PH-ILD patients with mild haemodynamic impairment may result in benefits in multiple clinically relevant outcomes and may prevent or delay disease progression as well as other untoward longer-term sequelae. Though the post hoc analyses in this study were not adequately powered to detect significant differences in subgroups, the direction and magnitude of effects of treatment on multiple outcomes were consistent in patients with mild haemodynamic impairment. These benefits are not reflected by changes in the 6MWT distance and underscore the importance of evaluating multiple disease domain endpoints. These findings also suggest the importance of screening, diagnosis and treatment of patients with PH-ILD regardless of their level of haemodynamic impairment. Further adequately powered studies of patients with PH-ILD with mild haemodynamics are needed to confirm these findings.
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Ethics approval Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

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