EUROPEAN RESPIRATORY *journal*

FLAGSHIP SCIENTIFIC JOURNAL OF ERS

Early View

Original research article

Long-term inhaled treprostinil for PH-ILD: INCREASE open-label extension study

Aaron Waxman, Ricardo Restrepo-Jaramillo, Thenappan Thenappan, Peter Engel, Abubakr Bajwa, Ashwin Ravichandran, Jeremy Feldman, Amy Hajari Case, Victor Tapson, Peter Smith, Chunqin Deng, Eric Shen, Steven D. Nathan

Please cite this article as: Waxman A, Restrepo-Jaramillo R, Thenappan T, *et al*. Long-term inhaled treprostinil for PH-ILD: INCREASE open-label extension study. *Eur Respir J* 2023; in press (https://doi.org/10.1183/13993003.02414-2022).

This manuscript has recently been accepted for publication in the *European Respiratory Journal*. It is published here in its accepted form prior to copyediting and typesetting by our production team. After these production processes are complete and the authors have approved the resulting proofs, the article will move to the latest issue of the ERJ online.

Copyright ©The authors 2023. For reproduction rights and permissions contact permissions@ersnet.org

Long-term Inhaled Treprostinil for PH-ILD: INCREASE Open-Label Extension Study

Aaron Waxman[1], Ricardo Restrepo-Jaramillo[2], Thenappan Thenappan[3], Peter Engel[4], Abubakr Bajwa[5], Ashwin Ravichandran[6], Jeremy Feldman[7], Amy Hajari Case[8], Victor Tapson[9], Peter Smith[10], Chunqin Deng[10], Eric Shen[10], Steven D. Nathan[11]

[1]Brigham and Women's Hospital, Boston, MA, USA. [2]University of South Florida, Tampa, FL, USA. [3]University of Minnesota, Minneapolis, MN, USA. [4]Carl and Edyth Lindner Research Center at the Christ Hospital, Cincinnati, OH, USA. [5]Ascension Medical Group, Jacksonville, FL, USA. [6]Ascension Medical Group, Indianapolis, IN, USA. [7]Arizona Pulmonary Specialists, Phoenix, AZ, USA. [8]Piedmont Healthcare, Atlanta, GA, USA. [9]Cedars-Sinai Medical Center, Los Angeles, CA, USA. [10]United Therapeutics, Research Triangle Park, NC, USA. [11]Inova Fairfax Hospital, Falls Church, VA, USA

Corresponding author:

Aaron B. Waxman, MD, PhD, FACP, FCCP

Pulmonary and Critical Care Medicine

Director, Pulmonary Vascular Disease Program

Executive Director, Center for Pulmonary-Heart Diseases

Brigham and Women's Hospital Heart and Vascular Center

Associate Professor of Medicine/Harvard Medical School

75 Francis Street, PBB CA-3

Boston, MA 02115 USA

E-mail: abwaxman@bwh.harvard.edu

Phone: 617-525-9733

Fax: 617-264-6873

Take-home Message

The INCREASE open-label extension supports the safety and efficacy of long-term treatment with inhaled treprostinil in patients with interstitial lung disease and associated pulmonary hypertension.

Target Journal: European Respiratory Journal

Journal limits: 3000 words, 8 figures and tables, 40 references, Abstr 250 words

Word counts: 3272 words [acceptable to journal per email], 6 figures, 2 tables, 26 references, Abstr 250 words

ABSTRACT [250 of 250 max]

Introduction

The 16-week randomised, placebo-controlled INCREASE trial (RCT) met its primary endpoint by improving 6-minute walk distance (6MWD) in patients receiving inhaled treprostinil for pulmonary hypertension due to interstitial lung disease (PH-ILD). The open-label extension (OLE) evaluated long-term effects of inhaled treprostinil in PH-ILD.

Methods

Of 258 eligible patients, 242 enrolled in the OLE and received inhaled treprostinil. Assessments included 6MWD, pulmonary function testing, N-terminal pro-brain natriuretic peptide (NT-proBNP), quality of life, and adverse events. Hospitalizations, exacerbations of underlying lung disease, and death were recorded.

Results

At OLE baseline, patients had a median age of 70 years and a mean 6MWD of 274.2 m; 52.1% were male. For the overall population, the mean 6MWD at week 52 was 279.1 m and the median change from RCT baseline was 3.5 m (22.1 m for the prior inhaled treprostinil arm, -19.5 m for the prior placebo arm); the median NT-proBNP decreased from 389 pg/mL at RCT baseline to 359 pg/mL at week 64; and the absolute (% predicted) mean FVC change from RCT baseline to week 64 was 51 mL (2.8%). Patients who received inhaled treprostinil versus placebo in the RCT had a 31% lower relative risk of exacerbation of underlying lung disease in the OLE (hazard ratio=0.69 [95% confidence interval: 0.49–0.97]; p=0.03). Adverse events leading to drug discontinuation occurred in 54 (22.3%) patients.

Conclusion

These results support the long-term safety and efficacy of inhaled treprostinil in patients with PH-ILD and are consistent with the results observed in the INCREASE RCT.

INTRODUCTION

Pulmonary hypertension (PH) frequently complicates the course of most fibrosing interstitial lung diseases (ILDs) [1]. From 15% and up to 86% of patients with ILD may develop PH, which is then associated with further impaired exercise tolerance, decreased quality of life, and a poor prognosis [2,3]. Prior to March of 2021, no therapies were approved for treating PH due to ILD (PH-ILD). Vasodilators used for pulmonary arterial hypertension (PAH) have been utilised off-label with mixed success, sometimes even causing harm [4,5].

The INCREASE study was a randomised, double-blind, placebo-controlled, phase 3 trial (RCT) that evaluated the effectiveness of inhaled treprostinil, a prostacyclin analogue, on exercise tolerance in patients with PH-ILD [6]. In INCREASE, 326 patients were randomised to inhaled treprostinil or placebo for 16 weeks. Inhaled treprostinil was associated with a significant placebo-corrected improvement in the primary endpoint of 6-minute walk distance (6MWD) of 31.1 m at week 16, (95% confidence interval (CI) 16.9–45.4; $p<0.001$). Inhaled treprostinil led to improvements compared to placebo in important secondary endpoints, including decreased plasma N-terminal pro-brain natriuretic peptide (NT-proBNP) and decreased occurrence of clinical worsening. Additionally, in post hoc analyses, inhaled treprostinil was associated with placebo-corrected improvement in the forced vital capacity (FVC) [7] with fewer disease progression events [8]. Based on the INCREASE results, the United States Food and Drug Administration (FDA) approved inhaled treprostinil as the first treatment for PH-ILD.

The chronicity of ILD necessitates long-term treatment; therefore, understanding the safety of prolonged administration of inhaled treprostinil is of paramount importance. Patients from the INCREASE RCT were eligible to enrol in an open-label extension (OLE) to evaluate the long-term safety and efficacy of inhaled treprostinil in patients with PH-ILD. Herein we present the results of the INCREASE OLE.

METHODS

The INCREASE OLE (NCT02633293) was a multicentre study. All patients received inhaled treprostinil (figure 1). The primary objective was to provide inhaled treprostinil to eligible patients who participated in the INCREASE RCT. The secondary objectives were to assess the long-term safety and efficacy of inhaled treprostinil in patients with PH-ILD. The study protocol was approved by the institutional review board at each trial site. The study was conducted in accordance with the International Council for Harmonisation and Good Clinical Practice guidelines and was monitored for safety by an independent data monitoring committee. All participants provided written informed consent. The planned study duration was until all patients were in the OLE for 108 weeks after the 16-week parent trial (i.e. a total of 124 weeks) or until inhaled treprostinil was approved by the FDA for the treatment of patients with PH-ILD, upon which the study would be discontinued.

Patients

Eligible patients 1) had received study drug treatment for the duration of the 16-week INCREASE RCT and completed all scheduled study visits; or 2) had discontinued study drug due to clinical worsening during the INCREASE RCT and completed all remaining scheduled study visits; or 3) were enrolled in the INCREASE RCT and their participation was discontinued by the sponsor. Briefly, patients eligible for INCREASE were adults with ILD and group 3 PH diagnosed by right heart catheterization within 1 year before randomization and who had a 6MWD of at least 100 m. Patients with underlying connective tissue disease were required to have a baseline FVC of <70%. No approved therapy for PAH was permitted within 60 days of randomization [6]. New medications were allowed, but if a patient required infused prostacyclin lasting ≥29 days, they were discontinued from the OLE.

Treatment

In the OLE, all patients discontinued the treatment received during the RCT and received inhaled treprostinil at 0.6 mg/mL via an ultrasonic pulsed-delivery nebuliser at 6 μg per breath regardless of their assigned treatment arm in the RCT. To preserve prior blinding, all OLE patients initiated inhaled treprostinil at three breaths per session (bps; 18 μg) four times a day (QID). Recommended dose escalations were an additional 1 bps QID every 3 days, per the investigator's discretion, to a maximum of 15 bps (90 μg) QID as tolerated.

Assessments

In the OLE, patients were assessed at week 20 (i.e. 4 weeks into the OLE), week 28, and then every 12 weeks up to week 124. Initial assessments for the OLE were collected at the RCT study termination visit (week 16) prior to the initiation of inhaled treprostinil. These assessments included a physical examination, 6-minute walk test, pulse oximetry, pulmonary function tests (PFTs), St. George's Respiratory Questionnaire (SGRQ) [9], supplemental oxygen requirement, clinical laboratory assessments (serum electrolyte, chemistry, and haematology panels), serum NT-proBNP, urine pregnancy test, and adverse events (AEs). Hospitalizations, exacerbations of underlying lung disease, and death were recorded from the time of informed consent until study termination. Clinical worsening was assessed in the RCT but not recorded in the OLE as a pre-specified endpoint. The SGRQ and NT-proBNP were assessed at weeks 64 and 124 or study termination. PFTs were assessed at weeks 28, 64, and 124 or study termination. AEs were coded using MedDRA version 24.0.

Endpoints

There were no prespecified analyses as the objective of the OLE was to provide inhaled treprostinil to study patients and capture observational long-term safety and efficacy data in the open-label setting. The observational efficacy data captured included 6MWD, NT-proBNP, quality of life as measured by the

SGRQ, and change in distance saturation product (DSP) [10] from baseline to week 64 (or study discontinuation if earlier). The safety data collected included AEs; pulse oximetry and supplemental oxygen requirements; PFTs including the FVC, forced expiratory volume in 1 sec, total lung capacity (TLC), and lung diffusion capacity for carbon monoxide (DLco); clinical laboratory parameters; vital signs; hospitalizations due to a cardiopulmonary indication; exacerbations of underlying lung disease, defined as an acute, clinically significant, respiratory deterioration characterised by evidence of new widespread alveolar infiltrates on chest imaging; and death.

Statistical Methods

All analyses were performed on the safety population, defined as all patients who received inhaled treprostinil during the OLE. Descriptive statistics were used to summarise results. All new AEs with an onset date on or after the first dose of inhaled treprostinil in the OLE were tabulated. Time to exacerbation of lung disease, cardiopulmonary hospitalization, and death from the beginning of the OLE was analysed using the Kaplan-Meier method and log-rank test comparing patients by prior treatment assignment in the RCT. A Cox regression model was used to obtain hazard ratios (HRs) with prior treatment as an explanatory variable.

RESULTS

A total of 243 patients enrolled in the INCREASE OLE (figure 2), of whom 242 received at least one dose of study drug and were included in the safety population. Two patients were excluded from the INCREASE RCT analysis due to a study drug labelling issue and enrolled directly into the OLE as allowed by the study protocol; the remaining 240 patients were previously enrolled and analysed in the INCREASE RCT, representing 73.6% of the total RCT population (n=326) and 93.0% of the eligible analysed RCT population (n=258). Baseline characteristics of patients at the start of INCREASE OLE

reflected the differential treatment received during the INCREASE RCT, with mean 6MWD of 281.8 m in the inhaled treprostinil group and 266.3 m in the placebo group and median NT-proBNP of 1312.9 pg/ml in the inhaled treprostinil group and 3115.2 pg/ml in the placebo group (table 1). Overall, patients had a median of 0.9 years since the diagnosis of PH-ILD, and the most common ILD was idiopathic interstitial pneumonia (44.6%).

Exposure

Total median inhaled treprostinil exposure duration in the OLE was 62.1 weeks (77.3 weeks and 47.0 weeks in patients from the inhaled treprostinil group and placebo group of the RCT, respectively). The reduced exposure in the prior placebo group likely reflected a higher number of patients who discontinued study drug due to an AE in this group compared to the prior inhaled treprostinil group (table 2). Study drug dosing is summarised in figure S1. From week 28 to week 76, the median number of bps was 12 at all time points for both groups. Overall, 80.6%, 60.7%, and 26.9% of patients had achieved a maximum dose of ≥9, ≥12, and ≥15 bps QID, respectively, by the end of the study.

Efficacy

The mean (standard deviation [SD]) 6MWD at week 52 was 279.1 m (114.8) for the overall population, 286.2 (119.2) in the former inhaled treprostinil arm, and 270.3 m (109.5) in the former placebo arm. Mean 6MWD results by study visit (figure 3a) demonstrated that among patients who received inhaled treprostinil in the RCT, mean 6MWD increased from RCT baseline to week 16 and then during the OLE remained greater than RCT baseline through week 52. Patients who received placebo in the RCT experienced an increase in mean 6MWD at weeks 28 and 40 of the OLE after initiating inhaled treprostinil, and then a decrease in mean 6MWD from week 40 to week 52. When 6MWD was analysed as change from baseline of the RCT (figure 3b), the mean (SD) change at week 52 was 3.5 m (70.7) for

the overall population, 22.1 m (66.3) in the former inhaled treprostinil arm, and -19.5 m (69.8) in the former placebo arm.

For the overall population, median (interquartile range [IQR]) NT-proBNP decreased from 389 pg/mL (159-1763) at RCT baseline to 359 pg/mL (135-1551) at week 64. Results for each prior treatment arm are shown in Figure 4.

No deterioration in the SGRQ or DSP was observed during the OLE (tables S1 and S2, respectively).

Safety

AEs occurred in 229 patients (94.6%) during the OLE (table 2). Serious AEs occurred in 133 patients (55.0%). AEs leading to drug discontinuation occurred in 54 patients (22.3%), with a higher incidence occurring in patients who had previously received placebo rather than inhaled treprostinil (28.1% vs. 16.8%, respectively). Consistent with the RCT, the most common AEs were cough, dyspnoea, and headache. Patients previously on placebo were more likely than patients previously on inhaled treprostinil to experience cough and headache.

For the overall population, the mean change from RCT baseline in FVC at week 64 was 51 mL, corresponding to a mean (SD) increase of 2.8 (8.6)% in percent predicted FVC. Results for each prior treatment arm are shown in figure 5. FVC changes for the four most common ILD subtypes are shown in figure S2. No other changes in PFTs were observed during the OLE (table S3), and no clinically relevant treatment-related changes in blood oxygen saturation (table S4) or supplemental oxygen use occurred (table S5).

Overall, 133 (55.0%) patients experienced at least one exacerbation of underlying lung disease during the OLE. The Kaplan-Meier estimate of time to first exacerbation of underlying lung disease from the

start of the OLE was significantly prolonged among patients who previously received inhaled treprostinil compared with patients who previously received placebo (HR, 0.69 [95% CI 0.49–0.97]; p=0.0321; median 67.0 weeks versus 32.9 weeks) (figure 6a). This translates to a 31% reduction in acute exacerbations for the former inhaled treprostinil group compared to the former placebo arm. In a Cox regression analysis incorporating adjustments for sex, age, and baseline pulmonary vascular resistance (PVR), patients formerly on inhaled treprostinil had a significantly reduced risk for exacerbation (HR 0.70 [95% CI 0.49–0.99]; p=0.0437). Time to first exacerbation from the start of the RCT is shown in figure 6b.

During the OLE, 76 patients (31.4%) experienced a cardiopulmonary hospitalization. There was no significant difference in time to cardiopulmonary hospitalization between the prior active compared to the prior placebo arm (HR, 0.90 [95% CI 0.57–1.41]; p=0.64). Sixty-two patients (25.6%) died during the OLE. Patients in the prior active arm had a numerically reduced risk of death compared with the prior placebo arm, but the difference was not statistically significant (HR, 0.67 [95% CI 0.41–1.11]; p=0.12). Among the patients who died, 29 patients (24.4%) who had previously received inhaled treprostinil had a median time to death of 62.0 weeks compared to 31.3 weeks in the 33 patients (27.3%) who had previously received placebo. Kaplan-Meier estimates of median time to event for cardiopulmonary hospitalizations and deaths could not be calculated due to the low number of events.

DISCUSSION

The development of PH in patients with ILD portends a poor prognosis. The COMPERA registry reported estimated 5-year survival rates of 14.0% in patients with PH-ILD compared with 51.8% in patients with idiopathic PAH [11]. Data from a Danish centre demonstrated an eightfold increased risk of death among ILD patients who developed PH compared with those who did not [12]. Prior to INCREASE, data with vasodilators led to conflicting results [5]. The largest RCT in patients with PH-ILD prior to INCREASE,

the RISE-IIP trial of riociguat, demonstrated a lack of clinical benefit and had increased serious AEs and deaths in the active treatment arm [4].

In the INCREASE RCT, 16 weeks of inhaled treprostinil therapy was associated with improvements in 6MWD, NT-proBNP, and time to clinical worsening, demonstrating a substantial advance in treating this challenging disease [6]. The INCREASE OLE demonstrated minimal decline in exercise capacity for up to 52 weeks. Levels of NT-proBNP, a biomarker associated with morbidity and mortality in PH [13], as well as clinical status and pulmonary haemodynamics in patients with ILD [14], decreased in patients transitioning from placebo to inhaled treprostinil and remained stable in patients previously assigned to active treatment in the parent trial. Lastly, oxygenation data continued to demonstrate that ventilation-perfusion mismatch is not a significant concern even with long-term inhaled treprostinil use in patients with PH-ILD.

Upon further assessment of the 6MWD results by prior treatment arm, it is encouraging to observe the stabilization of 6MWD in patients formerly randomised to inhaled treprostinil. However, the 6MWD results for the patients formerly on placebo are mixed: the mean 6MWD improved at weeks 28 and 40, suggesting that patients derived benefit once they started inhaled treprostinil, but this improvement was not sustained at week 52 (figure 3a). When analysing 6MWD as the change from baseline of the RCT (figure 3b), there is only slight deterioration observed during the OLE during which patients are receiving inhaled treprostinil. From the RCT baseline, the mean change at week 52 was 22.1 m in the former inhaled treprostinil arm, and -19.5 m in the former placebo arm. By comparison, data from other studies in similar ILD patient populations suggest that 6MWD decreases quite dramatically when patients are left untreated on placebo, with mean declines of 45.2 m (12 weeks) and 53.1 m (16 weeks) [15, 16]. Therefore, the lack of significant deterioration observed in the INCREASE OLE could be considered a marker of efficacy in the context of the progressive nature of PH-ILD.

One possible interpretation of these two methods of evaluating 6MWD is that earlier intervention impacts 6MWD improvement; patients who received placebo in the RCT and thus had a 16-week delay in treatment did not achieve the same benefit at week 52 as the group originally randomised to inhaled treprostinil. However, real-world application of this finding may be difficult in light of the varied course of ILD progression and PH onset. As there is no true comparator group in the OLE, and no follow-up pulmonary hemodynamic data, the impact of earlier treatment in PH-ILD remains a topic of future research.

The increase in FVC among patients who had previously received inhaled treprostinil in the RCT demonstrated durability during the OLE with no substantial changes observed. For patients who had received placebo in the RCT, a numerical increase in FVC was demonstrated once starting inhaled treprostinil in the OLE. This finding is notable in that clinical studies of other ILD therapies have generally shown a slowing of the decline in lung function, with FVC loss being numerically greater in the placebo group compared with active therapy [17,18]. By contrast, in both the INCREASE RCT and OLE, there is an overall increase in mean FVC after initiating inhaled treprostinil. The FVC increase in the former placebo arm is intriguing as it replicates the change seen in the active arm of the parent study. This observation lends support to the study of the antifibrotic properties of treprostinil. [19] Other potential, albeit speculative, hypotheses that could explain this FVC increase might be improved pulmonary vascular compliance or improved blood flow and respiratory muscle strength. Regarding other PFTs, there was no clinically significant change in DLco or TLC (table S3).

At present, it is unclear why the FVC increase seen in the OLE is not accompanied by a similarly strong improvement in exercise capacity. The 6MWD results could reflect the deconditioning associated with the 16-week treatment delay that is not reflected in lung function. For instance, the treatment delay may have impacted muscle physiology, muscle perfusion, and perfusion-metabolism matching; the

incomplete transition to 6MWD benefit could possibly be due to a treatment delay adversely affecting the patients' ability to exercise. Furthermore, this trial was conducted during COVID-19 restrictions. Many pulmonary rehabilitation programs were inaccessible, and patients may have been unable to exercise. Randomised trials have demonstrated the benefit of exercise training in patients with both ILD [20, 21] and PAH [22, 23], and a lack of ongoing access to programs may have impacted the 6MWD results.

Earlier treatment with inhaled treprostinil may have led to benefits in clinical outcomes in the OLE as well. Prior treatment with inhaled treprostinil was associated with a significant 31% reduction in the risk of exacerbations when compared to prior treatment with placebo. One post hoc analysis of the INCREASE OLE showed that treatment with inhaled treprostinil in the RCT resulted in improved event-free survival, defined as the composite of time to first hospitalization, exacerbation, or death when compared to placebo [24]. These results suggest that early screening and diagnosis of PH in patients with ILD need to be studied systematically. . A Delphi consensus study has been recently published that can aid clinicians in screening for PH in patients with ILD [25] and there is an ongoing prospective clinical trial to elucidate PH screening strategies in this patient population [26].

The safety of inhaled treprostinil in the OLE is consistent with the 16-week trial [6], with the encouraging finding of improvement in tolerability over time. Patients in the inhaled treprostinil arm of the RCT experienced reduced rates of cough (18.5% versus 35.5%) and headache (10.1% versus 27.3%) during the OLE compared with those who initiated inhaled treprostinil in the OLE. This finding attests to the possible attenuation of these AEs over time and, together with the outcomes data, support persistence with the medication while trying to manage AEs. Indeed, one post hoc analysis of INCREASE OLE safety data shows that the majority of patients reported recovery or resolution of the most common AEs in the study [27].

The primary strength of the current trial was its extended duration, providing information on long-term treatment with inhaled treprostinil. Limitations of the OLE were the open-label design which limits data interpretation; without a placebo arm, the varying degree of responses between different endpoints (e.g. 6MWD vs. FVC) can be challenging to interpret. In addition, analysis of the results is limited by the small number of subjects with evaluable data at the end of the OLE period, and patients have varying periods of follow-up. There is a high probability of deteriorating patients being among those who discontinued the study early and no imputation was employed to account for this.

In conclusion, the INCREASE OLE demonstrated the safety of long-term inhaled treprostinil in patients with PH-ILD. No new safety signals were observed, and the rate of cough decreased with a longer treatment duration. The safety profile was accompanied by maintained exercise capacity and increased FVC, despite challenges associated with the COVID-19 pandemic. Overall, these long-term results are consistent with the findings from the parent INCREASE study, and lend further support to the study of the potential antifibrotic effects of inhaled treprostinil.

ACKNOWLEDGEMENTS

The authors would like to thank Laura Evans, PharmD with Twist Medical for assistance with manuscript preparation and editing that was funded by United Therapeutics. We would also like to thank all INCREASE study centres, research staff, and patients for participating in this trial.

FINANCIAL SUPPORT

Funding for the study was provided by United Therapeutics.

TABLES

Table 1. Baseline characteristics for subjects in the INCREASE OLE.[a]

	Received Inhaled Treprostinil in RCT N=119	**Received Placebo in RCT N=121**	**Overall N=242[b]**
Age, median (range), years	70.0 (27–90)	71.0 (36–86)	70.0 (27–90)
Female, n (%)	63 (52.9)	52 (43.0)	116 (47.9)
Race or ethnicity, n (%)			
White	78 (65.5)	98 (81.0)	178 (73.6)
Black or African American	33 (27.7)	20 (16.5)	53 (21.9)
American Indian or Alaska Native	2 (1.7)	1 (0.8)	3 (1.2)
Asian	6 (5.0)	2 (1.7)	8 (3.3)
Hispanic or Latino	7 (5.9)	10 (8.3)	17 (7.0)
Time since PH-ILD diagnosis, mean (SD), years	0.9 (1.1)	0.9 (1.5)	0.9 (1.3)
Current ILD diagnosis, n (%)			
Idiopathic interstitial pneumonia	47 (39.5)	61 (50.4)	108 (44.6)
Combined pulmonary fibrosis and emphysema	29 (24.4)	29 (24.0)	59 (24.4)
Connective tissue disease	33 (27.7)	24 (19.8)	57 (23.6)
Chronic hypersensitivity pneumonitis	7 (5.9)	6 (5.0)	13 (5.4)
Occupational lung disease	3 (2.5)	1 (0.8)	5 (2.1)
Idiopathic interstitial pneumonia subcategory, n %			
Idiopathic pulmonary fibrosis	25 (21.0)	42 (34.7)	67 (27.7)

	Received Inhaled Treprostinil in RCT N=119	Received Placebo in RCT N=121	Overall N=242[b]
Idiopathic nonspecific interstitial pneumonia	16 (13.4)	13 (10.7)	29 (12.0)
Respiratory bronchiolitis associated with ILD	2 (1.7)	0	2 (0.8)
Desquamative interstitial pneumonia	0	1 (0.8)	1 (0.4)
Acute interstitial pneumonia	0	1 (0.8)	1 (0.4)
Unclassified idiopathic interstitial pneumonia	4 (3.4)	4 (3.3)	8 (3.3)
6MWD, mean (SD), m	281.8 (99.6)	266.3 (113.2)	274.2 (106.3)
6MWD, mean (SD), m at the start of the 16-week RCT	256.2 (101.3)	269.5 (90.1)	262.0 (95.9)
FVC % predicted, mean (SD), %	64.7 (22.3)	63.4 (19.7)	64.3 (21.1)
NT-proBNP, mean (SD), pg/mL	1312.9 (2242.8)	3115.2 (9461.4)	2231.9 (6943.0)
Antifibrotic therapy, n (%)			
None	100 (84.0)	88 (72.7)	190 (78.5)
Pirfenidone only	12 (10.1)	18 (14.9)	30 (12.4)
Nintedanib only	7 (5.9)	15 (12.4)	22 (9.1)

FVC: forced vital capacity; OLE: open-label extension; RCT: randomised controlled trial; PH-ILD: pulmonary hypertension due to interstitial lung disease; SD: standard deviation; 6MWD: 6-minute walk distance; NT-proBNP: N-terminal pro-brain natriuretic peptide. [a]Baseline is defined as the last measurement prior to the first dose of inhaled treprostinil in the INCREASE OLE study unless otherwise specified. Baseline data from the RCT have been previously published [6]. [b]Two patients were not previously enrolled in the RCT.

Table 2. Adverse events during INCREASE OLE.

	Received Inhaled Treprostinil in RCT N=119	Received Placebo in RCT N=121	Overall N=242[a]
Number of patients with at least 1 AE, n (%)	112 (94.1)	115 (95.0)	229 (94.6)
Total number of adverse events (AE rate,[b] %)	1085 (6.7)	993 (7.9)	2091 (7.2)
Number of patients with at least 1 SAE, n (%)	66 (55.5)	65 (53.7)	133 (55.0)
Number of patients with at least 1 AE leading to discontinuation of inhaled treprostinil, n (%)	20 (16.8)	34 (28.1)	54 (22.3)
AEs occurring in >10% of all patients, n (%)			
Cough	22 (18.5)	43 (35.5)	65 (26.9)
Dyspnoea	30 (25.2)	33 (27.3)	63 (26.0)
Headache	12 (10.1)	33 (27.3)	45 (18.6)
Diarrhoea	20 (16.8)	17 (14.0)	37 (15.3)
Dizziness	18 (15.1)	18 (14.9)	36 (14.9)
Upper respiratory tract infection	20 (16.8)	14 (11.6)	34 (14.0)
Nausea	18 (15.1)	14 (11.6)	32 (13.2)
Fatigue	18 (15.1)	14 (11.6)	32 (13.2)
Pneumonia	14 (11.8)	15 (12.4)	30 (12.4)
Acute respiratory failure	16 (13.4)	14 (11.6)	30 (12.4)
Urinary tract infection	10 (8.4)	15 (12.4)	27 (11.2)
Back pain	16 (13.4)	10 (8.3)	26 (10.7)
Productive cough	8 (6.7)	16 (13.2)	25 (10.3)

OLE: open-label extension; RCT: randomised controlled trial; AE: adverse event; SAE: serious adverse event. [a]Two patients were not previously enrolled in the RCT. [b]AE rate calculated as the number of AEs divided by the total number of patient-years per treatment group. Total patient-years were 160.91 years for patients previously treated with inhaled treprostinil, 126.46 years for previously treated with placebo, and 289.84 years overall.

REFERENCES

1 Humbert M, Kovacs G, Hoeper MM, et al. 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Respir J* 2023; 61: 2200879.

2 Nathan SD. Pulmonary hypertension in interstitial lung disease. *Int J Clin Pract* 2008; 62: 21–28.

3 Nathan SD, Hassoun PM. Pulmonary hypertension due to lung disease and/or hypoxia. *Clin Chest Med* 2013; 34: 695–705.

4 Nathan SD, Behr J, Collard HR, *et a*l. Riociguat for idiopathic interstitial pneumonia-associated pulmonary hypertension (RISE-IIP): a randomised, placebo-controlled phase 2b study. *Lancet Respir Med* 2019; 7: 780–790.

5 Nathan SD, Barbera JA, Gaine SP, *et al*. Pulmonary hypertension in chronic lung disease and hypoxia. *Eur Respir J* 2019;53:1801914.

6 Waxman A, Restrepo-Jaramillo R, Thenappan T, *et al*. Inhaled treprostinil in pulmonary hypertension due to interstitial lung disease. *N Engl J Med* 2021; 384: 325–334.

7 Nathan SD, Waxman A, Rajagopal S, *et al*. Inhaled treprostinil and forced vital capacity in patients with interstitial lung disease and associated pulmonary hypertension: a post-hoc analysis of the INCREASE study. *Lancet Respir Med* 2021; 9: 1266–1274.

8 Nathan SD, Tapson VF, Elwing J, *et al*. Efficacy of inhaled treprostinil on multiple disease progression events in patients with pulmonary hypertension due to parenchymal lung disease in the INCREASE trial. *Am J Respir Crit Care Med* 2022; 205: 198–207.

9 Welling JB, Hartman JE, Ten Hacken NH, *et al*. The minimal important difference for the St George's Respiratory Questionnaire in patients with severe COPD. *Eur Respir J* 2015; 46: 1598–1604.

10 Lettieri CJ, Nathan SD, Browning RF, *et al*. The distance-saturation product predicts mortality in idiopathic pulmonary fibrosis. *Respir Med* 2006; 100: 1734–1741.

11 Hoeper MM, Behr J, Held M, *et al*. Pulmonary hypertension in patients with chronic fibrosing idiopathic interstitial pneumonias. *PLoS One* 2015; 10: e0141911.

12 Andersen CU, Mellemkjær S, Hilberg O, *et al*. Pulmonary hypertension in interstitial lung disease: prevalence, prognosis and 6 min walk test. *Respir Med* 2012; 106: 875–882.

13 Galiè N, Jansa P, Pulido T, *et al*. SERAPHIN haemodynamic substudy: the effect of the dual endothelin receptor antagonist macitentan on haemodynamic parameters and NT-proBNP levels and their association with disease progression in patients with pulmonary arterial hypertension. *Eur Heart J* 2017; 38: 1147–1155.

14 Leuchte HH, Baumgartner RA, Nounou ME, *et al*. Brain natriuretic peptide is a prognostic parameter in chronic lung disease. *Am J Respir Crit Care Med* 2006; 173: 744–750.

15 Idiopathic Pulmonary Fibrosis Clinical Research Network, Zisman DA, Schwarz M, et al. A controlled trial of sildenafil in advanced idiopathic pulmonary fibrosis. *N Engl J Med* 2010; 363: 620–628.

16 Corte TJ, Keir GJ, Dimopoulos K, *et al*. Bosentan in pulmonary hypertension associated with fibrotic idiopathic interstitial pneumonia. *Am J Respir Crit Care Med* 2014; 190: 208–217.

17 Noble PW, Albera C, Bradford WZ, *et al*. Pirfenidone for idiopathic pulmonary fibrosis: analysis of pooled data from three multinational phase 3 trials. *Eur Respir J* 2016; 47: 243–253.

18 Flaherty KR, Kolb M, Vancheri C, *et al*. Stability or improvement in forced vital capacity with nintedanib in patients with idiopathic pulmonary fibrosis. *Eur Respir J* 2018; 52: 1702593.

19 Kolb M, Orfanos SE, Lambers C, *et al*. The antifibrotic effects of inhaled treprostinil: an emerging option for ILD. *Adv Ther* 2022; 39: 3881–3895.

20 Dowman LM, McDonald CF, Hill CJ, *et al*. The evidence of benefits of exercise training in interstitial lung disease: a randomised controlled trial. *Thorax* 2017; 72: 610–619.

21 Vainshelboim B, Oliveira J, Yehoshua L, *et al*. Exercise training-based pulmonary rehabilitation program is clinically beneficial for idiopathic pulmonary fibrosis. *Respiration* 2014; 88: 378–388.

22 Kagioglou O, Mouratoglou SA, Giannakoulas G, *et al*. Long-term effect of an exercise training program on physical functioning and quality of life in pulmonary hypertension: a randomized controlled trial. *Biomed Res Int* 2021; 2021: 8870615.

23 Grünig E, MacKenzie A, Peacock AJ, *et al*. Standardized exercise training is feasible, safe, and effective in pulmonary arterial and chronic thromboembolic pulmonary hypertension: results from a large European multicentre randomized controlled trial. *Eur Heart J* 2021; 42: 22842295.

24 Nathan SD, Argula R, Rajagopal, *et al*. Inhaled treprostinil in patients with pulmonary hypertension due to interstitial lung disease: event-free survival in INCREASE study open-label extension. *Eur Resp J* 2022; 60 (suppl 66):2133. DOI: 10.1183/13993003.congress-2022.2133

25 Rahaghi FF, Kolaitis NA, Adegunsoye A, *et al*. Screening strategies for pulmonary hypertension in patients with interstitial lung disease: a multidisciplinary Delphi study. *Chest* 2022; 162: 145–155.

26 Clinicaltrials.gov. Pulmonary hypertension screening in patients with interstitial lung disease for earlier detection (PHINDER). March 20, 2023. Accessed March 27, 2023. https://clinicaltrials.gov/ct2/show/NCT05776225?term=phinder&draw=2&rank=1

27 Waxman AB, Elwing J, Melendres-Groves L, *et al*. Long-term safety and tolerability of inhaled treprostinil in patients with pulmonary hypertension associated with interstitial lung disease in the INCREASE open-label extension. Poster presented at the CHEST Annual Meeting; Oct 16–19, 2022; Nashville, TN.

FIGURE LEGENDS

Figure 1. INCREASE study schema. RCT: randomised controlled trial; OLE: open-label extension; bps: breaths per session; QID: four times a day. [a]Two additional patients entered the OLE who were excluded from the INCREASE RCT due to a labelling issue. [b]Patients receiving >3 bps QID at week 16 of INCREASE RCT had their dose reduced to 3 bps QID at the start of the INCREASE OLE.

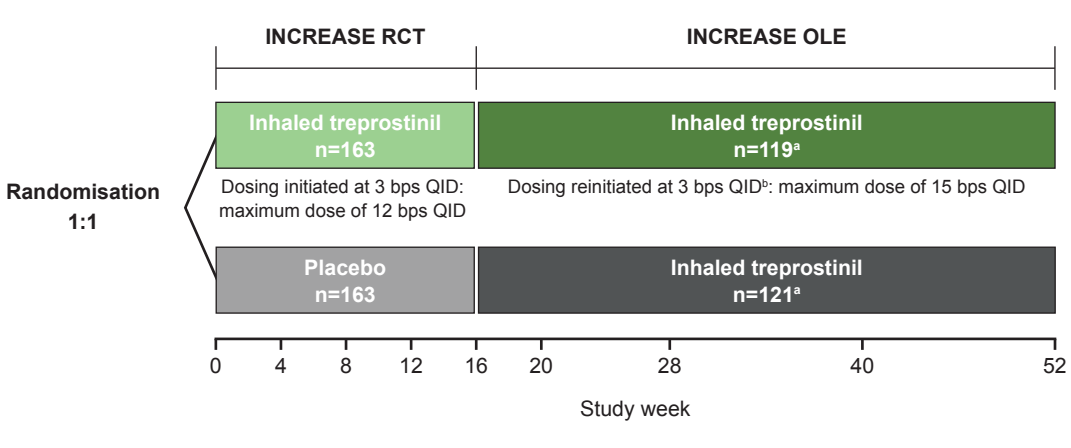
Figure 2. Patient disposition diagram. RCT: randomised controlled trial; OLE: open-label extension. [a]Completed 16 weeks of assessment in the INCREASE RCT. [b]Includes two patients who were excluded from the INCREASE RCT due to a labelling issue. [c]One patient was inadvertently enrolled in the INCREASE OLE after not meeting eligibility criteria but withdrew from the OLE before receiving study drug.

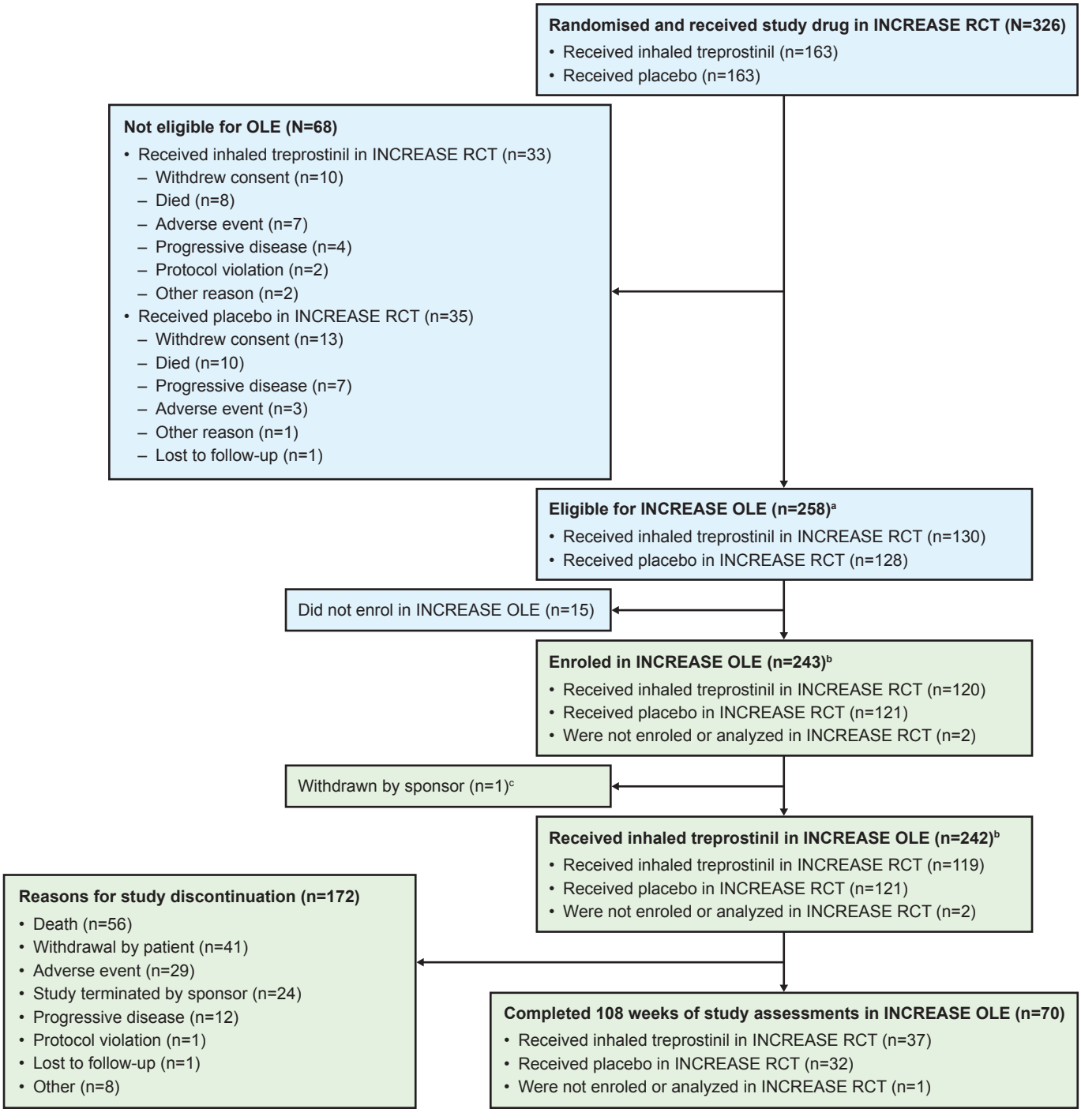
Figure 3. Six-minute walk distance (6MWD) results. a) Mean 6MWD by study visit starting from baseline of the 16-week INCREASE randomised controlled trial (RCT). Data are mean observed values. b) Mean change from baseline in 6MWD by study visit starting at baseline of the 16-week INCREASE RCT. Note: Time 0 for the OLE is also week 16 for the RCT; all available data at each time point are included in the figure. Errors bars indicate the standard error of the mean.

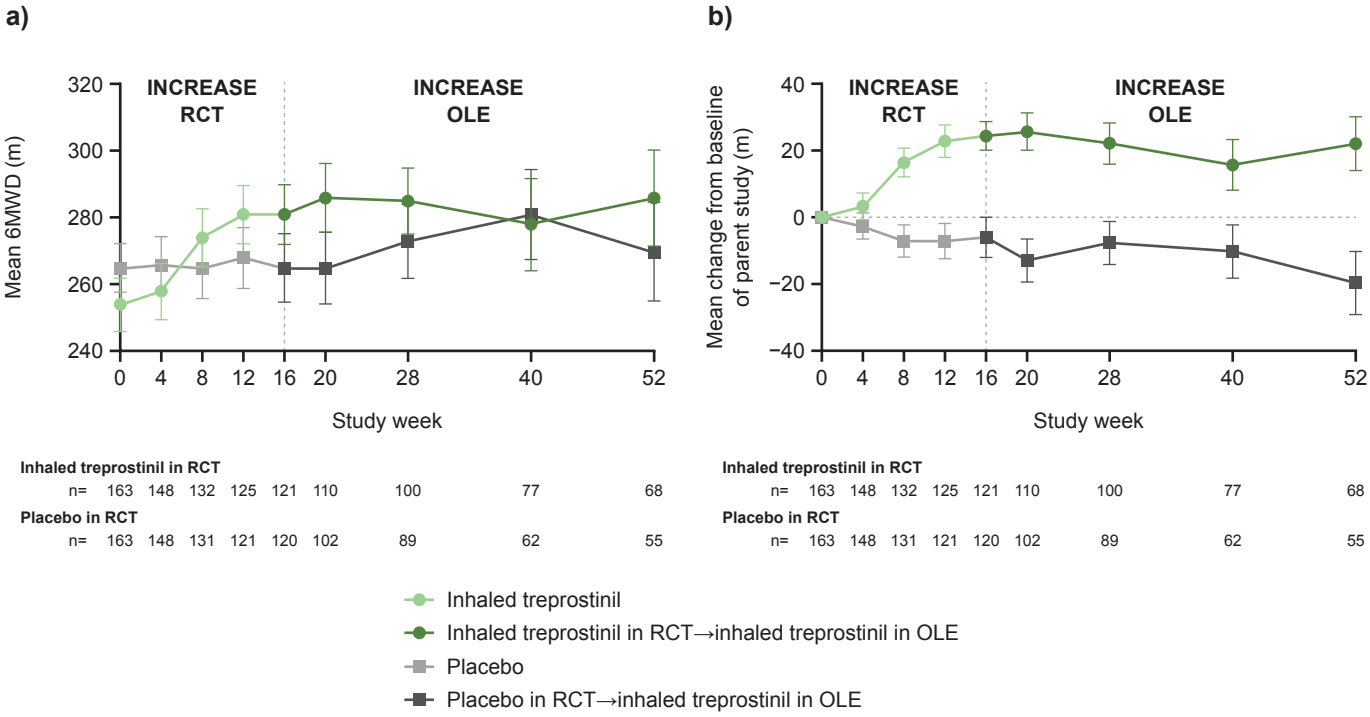
Figure 4. Median N-terminal pro-brain natriuretic peptide (NT-proBNP) serum levels during the INCREASE randomised controlled trial (RCT) and open-label extension (OLE) in patients who received inhaled treprostinil or placebo during the RCT. IQR: interquartile range.

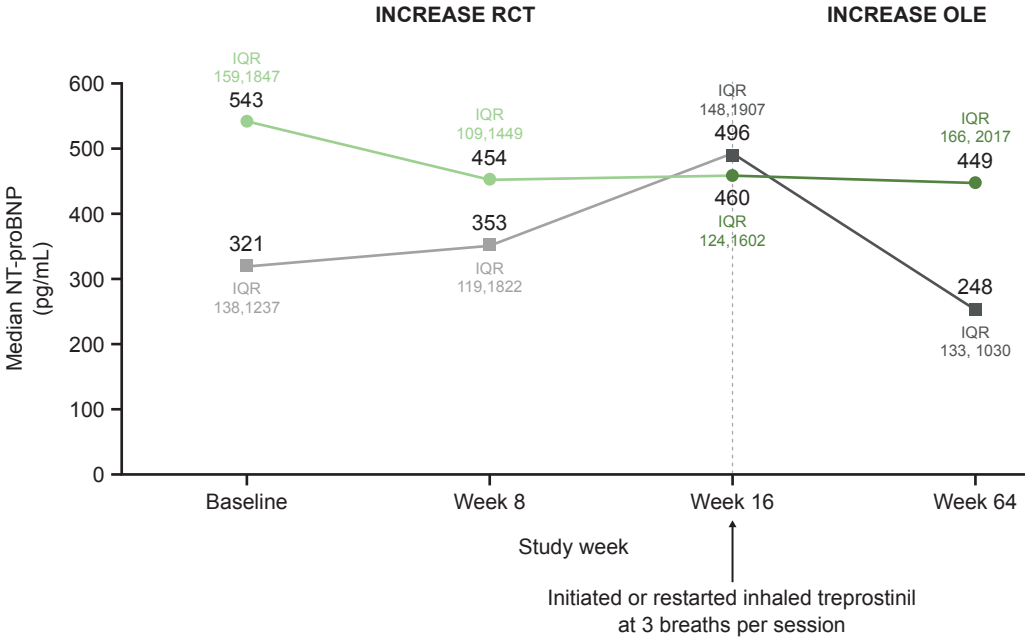
Figure 5. Mean change from baseline in forced vital capacity (FVC) in a) millilitres and as b) percent predicted in the INCREASE randomised controlled trial (RCT) and open-label extension (OLE). Note: Time 0 for the OLE is also week 16 for the RCT; all available data at each time point are included in the figure.

Figure 6. Kaplan-Meier estimates of time to exacerbation of lung disease from a) the INCREASE open-label extension (OLE) baseline (week 16) in all patients and b) the INCREASE randomized controlled trial (RCT) baseline (week 0) in all patients. In panel a, the Kaplan-Meier plot includes only exacerbations taking place in the OLE; therefore, all patients in both the prior inhaled treprostinil arm and the prior placebo arm are represented without an event at week 16. [a]Hazard ratio (HR), 95% confidence interval (CI), and p-value were calculated from a Cox proportional hazards model with the parent study treatment group as an explanatory variable.


INCREASE RCT
INCREASE OLE
Randomisation
1:1
Inhaled treprostinil
n=163
Inhaled treprostinil
n=119[a]
Dosing initiated at 3 bps QID:
maximum dose of 12 bps QID
Dosing reinitiated at 3 bps QID[b]: maximum dose of 15 bps QID
Placebo
n=163
Inhaled treprostinil
n=121[a]
0
4
8
12
16
20
28
40
52
Study week


Randomised and received study drug in INCREASE RCT (N=326)
• Received inhaled treprostinil (n=163)
• Received placebo (n=163)
Not eligible for OLE (N=68)
• Received inhaled treprostinil in INCREASE RCT (n=33)
– Withdrew consent (n=10)
– Died (n=8)
– Adverse event (n=7)
– Progressive disease (n=4)
– Protocol violation (n=2)
– Other reason (n=2)
• Received placebo in INCREASE RCT (n=35)
– Withdrew consent (n=13)
– Died (n=10)
– Progressive disease (n=7)
– Adverse event (n=3)
– Other reason (n=1)
– Lost to follow-up (n=1)
Eligible for INCREASE OLE (n=258)[a]
• Received inhaled treprostinil in INCREASE RCT (n=130)
• Received placebo in INCREASE RCT (n=128)
Did not enrol in INCREASE OLE (n=15)
Enroled in INCREASE OLE (n=243)[b]
• Received inhaled treprostinil in INCREASE RCT (n=120)
• Received placebo in INCREASE RCT (n=121)
• Were not enroled or analyzed in INCREASE RCT (n=2)
Withdrawn by sponsor (n=1)[c]
Received inhaled treprostinil in INCREASE OLE (n=242)[b]
• Received inhaled treprostinil in INCREASE RCT (n=119)
• Received placebo in INCREASE RCT (n=121)
• Were not enroled or analyzed in INCREASE RCT (n=2)
Reasons for study discontinuation (n=172)
• Death (n=56)
• Withdrawal by patient (n=41)
• Adverse event (n=29)
• Study terminated by sponsor (n=24)
• Progressive disease (n=12)
• Protocol violation (n=1)
• Lost to follow-up (n=1)
• Other (n=8)
Completed 108 weeks of study assessments in INCREASE OLE (n=70)
• Received inhaled treprostinil in INCREASE RCT (n=37)
• Received placebo in INCREASE RCT (n=32)
• Were not enroled or analyzed in INCREASE RCT (n=1)

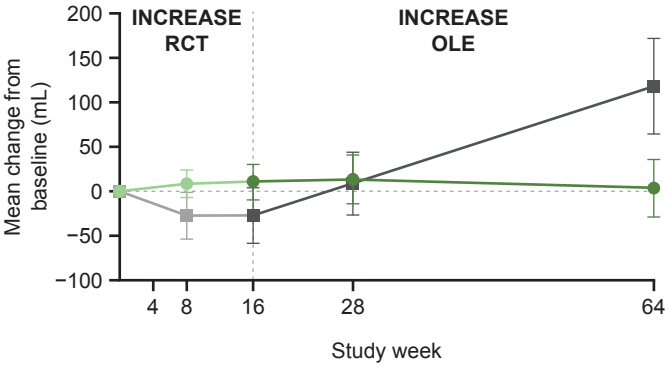

a)
b)
INCREASE RCT
INCREASE OLE
Mean 6MWD (m)
320
300
280
260
240
Mean change from baseline of parent study (m)
40
20
0
−20
−40
0 4 8 12 16 20 28 40 52
Study week
Inhaled treprostinil in RCT
n= 163 148 132 125 121 110 100 77 68
Placebo in RCT
n= 163 148 131 121 120 102 89 62 55
Inhaled treprostinil
Inhaled treprostinil in RCT→inhaled treprostinil in OLE
Placebo
Placebo in RCT→inhaled treprostinil in OLE



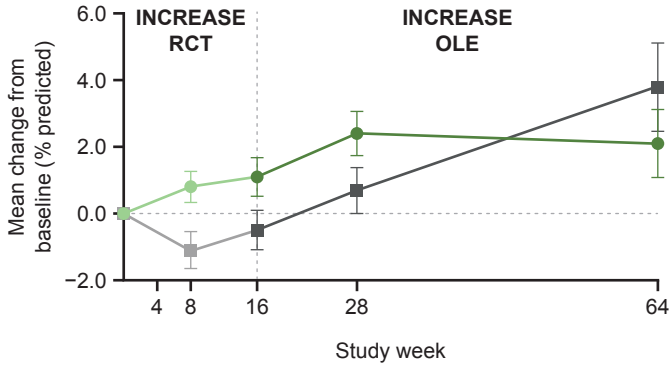
Inhaled treprostinil in RCT				
n=	115	115	111	85
Placebo in RCT				
n=	119	114	118	68

- Inhaled treprostinil
- Inhaled treprostinil in RCT→inhaled treprostinil in OLE
- Placebo
- Placebo in RCT→inhaled treprostinil in OLE

a) Change in FVC (mL)



b) Change in FVC (% predicted)

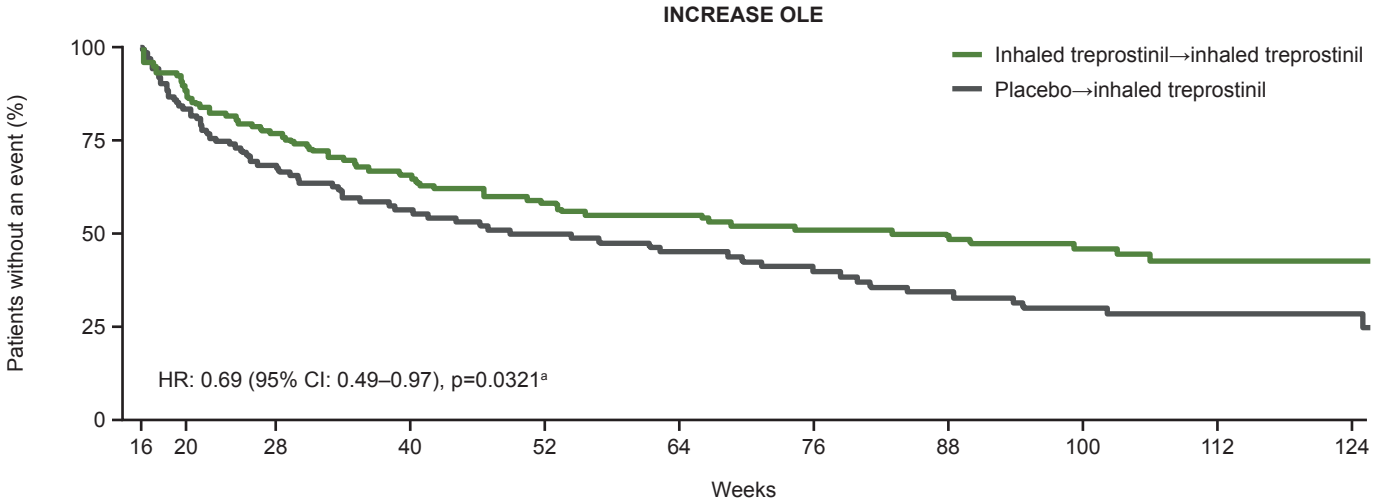


Inhaled treprostinil in RCT					
n=	162	141	129	100	46
Placebo in RCT					
n=	161	140	124	97	67

Inhaled treprostinil in RCT					
n=	162	141	129	100	46
Placebo in RCT					
n=	161	140	124	97	67

- Inhaled treprostinil
- Inhaled treprostinil in RCT→inhaled treprostinil in OLE
- Placebo
- Placebo in RCT→inhaled treprostinil in OLE

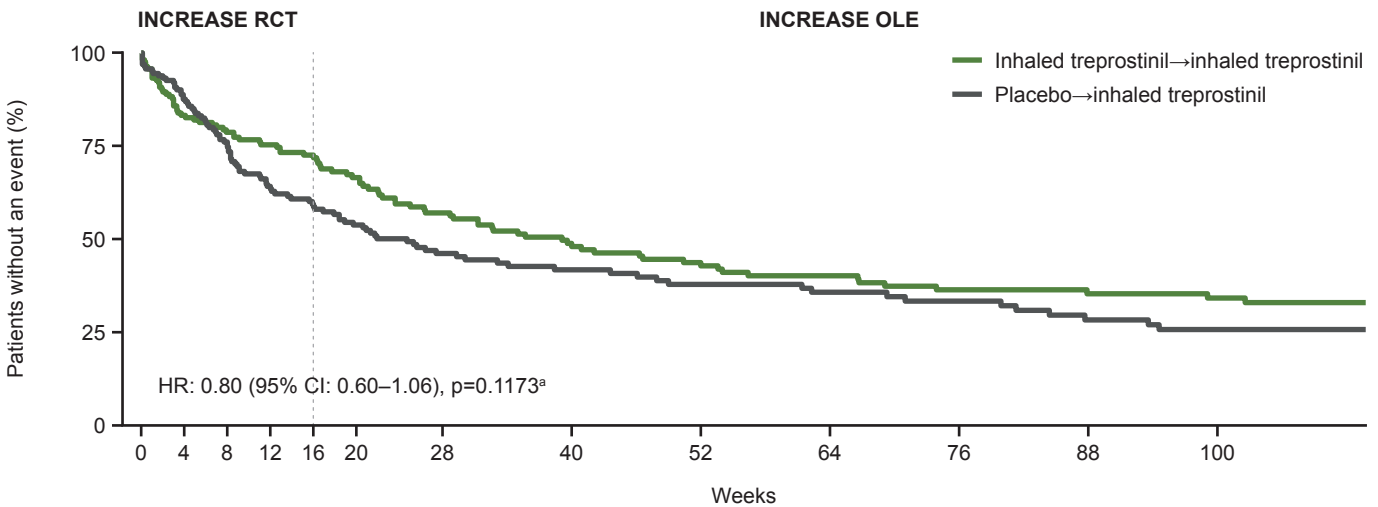
a)



No. at risk:

Inhaled treprostinil→inhaled treprostinil										
119	103	86	69	58	53	46	41	33	25	21
Placebo→inhaled treprostinil										
121	100	74	54	44	37	29	24	19	17	12

b)



No. at risk:

Inhaled treprostinil→inhaled treprostinil												
163	132	119	111	102	85	71	58	50	43	38	33	30
Placebo→inhaled treprostinil												
163	138	117	96	86	76	57	46	38	33	27	22	19

SUPPLEMENT

Long-term Inhaled Treprostinil for PH-ILD: INCREASE Open-Label Extension Study

Aaron Waxman[1], Ricardo Restrepo-Jaramillo[2], Thenappan Thenappan[3], Peter Engel[4], Abubakr Bajwa[5], Ashwin Ravichandran[6], Jeremy Feldman[7], Amy Hajari Case[8], Victor Tapson[9], Peter Smith[10], Chunqin Deng[10], Eric Shen[10], Steven D. Nathan[11]

[1]Brigham and Women's Hospital, Boston, MA, USA. [2]University of South Florida, Tampa, FL, USA. [3]University of Minnesota, Minneapolis, MN, USA. [4]Carl and Edyth Lindner Research Center at the Christ Hospital, Cincinnati, OH, USA. [5]Ascension Medical Group, Jacksonville, FL, USA. [6]Ascension Medical Group, Indianapolis, IN, USA. [7]Arizona Pulmonary Specialists, Phoenix, AZ, USA. [8]Piedmont Healthcare, Atlanta, GA, USA. [9]Cedars-Sinai Medical Center, Los Angeles, CA, USA. [10]United Therapeutics, Research Triangle Park, NC, USA. [11]Inova Fairfax Hospital, Falls Church, VA, USA

Contents

Table S1. St. George's Respiratory Questionnaire[a] Results

The St. George's Respiratory Questionnaire has a range of results from 0 to 100, with higher scores indicating greater impairment and with a minimum clinically important difference of 4 points.

	Received Inhaled Treprostinil in RCT N=119		**Received Placebo in RCT N=121**	
	Median Score (IQR)	**Mean Change from Week 16 (SD)**	**Median Score (IQR)**	**Mean Change from Week 16 (SD)**
Week 16[b]	55.3 (40.2–66.8) n=116	—	54.8 (46.3–69.4) n=118	—
Week 64	54.2 (39.8–69.3) n=84	0.8 (11.3) n=82	56.1 (44.7–70.2) n=71	1.3 (12.5) n=71
Week 124	46.0 (34.6–64.1) n=47	1.7 (13.0) n=45	56.0 (38.6–66.4) n=38	-3.2 (12.0) n=38

RCT: randomised controlled trial; IQR: interquartile range; SD: standard deviation. [a]Scores range from 0 to 100, with higher scores indicating worse quality of life [1].

[b]Week 16 reflects the baseline of the open-label extension (OLE). Baseline data from the RCT have been previously published [3].

Note: Due to drop outs and the variability of the data (i.e. large SDs and IQRs), the mean changes from baseline do not move in the same direction as the median values.

Table S2. Distance Saturation Product[a]

	Received Inhaled Treprostinil in RCT N=119		Received Placebo in RCT N=121	
	Median Score (IQR)	**Mean Change from Week 16 (SD)**	**Median Score (IQR)**	**Mean Change from Week 16 (SD)**
Week 16[b]	202.5 (153.9–275.4) n=109	—	210.6 (153.9–275.4) n=105	—
Week 64	218.7 (137.7–283.5) n=63	-16.2 (54.0) n=58	226.8 (170.1–267.3) n=40	-15.3 (52.8) n=37
Week 124	202.5 (153.9–287.6) n=28	-35.4 (64.6) n=27	210.6 (145.8–251.1) n=26	-19.7 (71.9) n=23

RCT: randomised controlled trial; IQR: interquartile range; SD: standard deviation. [a]Product of the 6-minute walk distance and the lowest room air oxygen saturation during the 6-minute walk test. Lower values indicate worse prognosis [2].

[b]Week 16 reflects the baseline of the OLE. Baseline data from the RCT have been previously published [3].

Note: Due to drop outs and the variability of the data (i.e. large SDs and IQRs), the mean changes from baseline do not move in the same direction as the median values.

Table S3. Pulmonary Function Test Results

	Received Inhaled Treprostinil in INCREASE RCT (n=119)				Received Placebo in INCREASE RCT (n=121)				All OLE Patients (N=242)			
Parameter Visit	n	Value, Mean (SD)	n	Change from Week 16, Mean (SD)	n	Value, Mean (SD)	n	Change from Week 16, Mean (SD)	n	Value, Mean (SD)	n	Change from Week 16, Mean (SD)
FEV1, L												
Week 16[a]	115	1.67 (0.66)	-	-	118	1.74 (0.54)	-	-	235	1.71 (0.61)	-	-
Week 28	100	1.65 (0.63)	96	-0.003 (0.18)	98	1.78 (0.56)	96	0.001 (0.27)	199	1.71 (0.60)	193	-0.000 (0.23)
Week 64	67	1.57 (0.61)	65	-0.007 (0.16)	46	1.79 (0.58)	45	-0.005 (0.36)	114	1.66 (0.61)	111	-0.007 (0.26)
FEV1 % Predicted, %												
Week 16[a]	115	64.4 (21.8)	-	-	118	64.8 (18.8)	-	-	235	64.7 (20.3)	-	-
Week 28	100	66.3 (21.0)	96	1.1 (5.8)	98	66.0 (19.0)	96	-0.3 (5.2)	199	66.2 (19.9)	193	0.4 (5.5)
Week 64	67	63.0 (18.6)	65	0.6 (7.4)	46	67.6 (20.7)	45	1.8 (7.8)	114	64.9 (19.5)	111	1.0 (7.6)
FVC, L												
Week 16[a]	115	2.26 (1.01)	-	-	118	2.28 (0.80)	-	-	235	2.28 (0.92)	-	-
Week 28	100	2.22 (0.98)	96	-0.024 (0.22)	98	2.34 (0.83)	96	0.009 (0.36)	199	2.28 (0.90)	193	-0.007 (0.30)

Week 64	67	2.12 (0.93)	65	-0.026 (0.24)	46	2.37 (0.87)	45	0.044 (0.47)	114	2.22 (0.90)	111	0.001 (0.35)
FVC % Predicted, %												
Week 16[a]	115	64.7 (22.3)	-	-	118	63.4 (19.7)	-	-	235	64.3 (21.1)	-	-
Week 28	100	66.1 (21.6)	96	0.3 (5.7)	98	65.7 (20.4)	96	0.3 (5.6)	199	66.0 (21.0)	193	0.3 (5.6)
Week 64	67	64.0 (19.8)	65	0.2 (8.2)	46	66.9 (21.3)	45	2.8 (6.7)	114	65.4 (20.4)	111	1.2 (7.7)
DLCO, mL/min/mmHg												
Week 16[a]	112	7.10 (3.26)	-	-	106	6.75 (3.10)	-	-	220	6.94 (3.17)	-	-
Week 28	97	6.92 (3.04)	92	-0.37 (2.91)	90	6.99 (3.18)	85	-0.21 (2.53)	188	6.97 (3.09)	178	-0.30 (2.72)
Week 64	65	7.18 (3.75)	63	-0.078 (2.65)	43	7.83 (3.19)	40	-0.06 (2.20)	109	7.44 (3.52)	104	-0.08 (2.47)
DLCO % Predicted, %												
Week 16[a]	112	28.8 (11.6)	-	-	106	26.9 (11.1)	-	-	220	28.0 (11.4)	-	-
Week 28	97	29.2 (13.0)	92	-1.0 (5.2)	90	28.5 (12.3)	85	0.2 (6.4)	188	29.0 (12.7)	178	-0.4 (5.8)
Week 64	65	29.5 (12.4)	63	-0.8 (7.2)	42	31.8 (12.1)	39	0.4 (9.2)	108	30.5 (12.3)	103	-0.4 (8.0)
TLC, L												
Week 16[a]	111	3.85 (1.53)	-	-	108	3.83 (1.17)	-	-	221	3.86 (1.38)	-	-

Week 28	95	3.78 (1.49)	90	0.008 (0.58)	86	3.85 (1.13)	81	-0.04 (0.54)	182	3.82 (1.33)	172	-0.013 (0.56)
Week 64	60	3.82 (1.47)	58	0.10 (0.70)	42	3.80 (1.17)	38	-0.10 (0.65)	103	3.82 (1.34)	97	0.022 (0.68)
TLC % Predicted, %												
Week 16[a]	111	66.9 (21.6)	-	-	108	63.8 (16.9)	-	-	221	65.6 (19.5)	-	-
Week 28	95	66.9 (18.5)	90	-0.1 (13.9)	85	65.8 (16.2)	80	-0.1 (7.2)	181	66.6 (17.6)	171	-0.1 (11.2)
Week 64	60	67.7 (21.6)	58	3.0 (14.5)	42	66.0 (18.6)	38	-0.5 (6.5)	103	67.3 (20.5)	97	1.6 (12.0)

RCT: randomised controlled trial; OLE: open-label extension; SD: standard deviation; FEV1: forced expiratory volume in 1 sec; FVC: forced vital capacity; DLCO: lung diffusion capacity for carbon monoxide; TLC: total lung capacity.

[a]Week 16 reflects the baseline of the OLE. Baseline data from the RCT have been previously published [3].

Table S4. SpO_2 (%) Measured by Pulse Oximetry by Visit

Visit Time Point Value	Received Inhaled Treprostinil in INCREASE RCT (n=119)		Received Placebo in INCREASE RCT (n=121)		All OLE Patients (N=242)	
	Value	Change from Pre-Walk	Value	Change from Pre-Walk	Value	Change from Pre-Walk
Week 16[a]						
Pre-walk						
N	114		113		229	
Mean (SD)	94.5 (4.5)		94.5 (4.3)		94.5 (4.3)	
Median	95.0		95.0		95.0	
Min–max	74.0–100.0		78.0–100.0		74.0–100.0	
During walk						
N	109	112	106	108	217	222
Mean (SD)	76.4 (7.8)	-18.0 (6.8)	78.4 (8.8)	-16.25 (8.6)	77.5 (8.3)	-17.1 (7.7)
Median	76.0	-18.0	79.0	-16.0	78.0	-17.0
Min–max	46.0–99.0	-38.0 to -1.0	28.0–98.0	-61.0 to -1.0	28.0–99.0	-61.0 to -1.0
Post-walk						
n	113	117	113	115	228	234

Mean (SD)	82.0 (9.3)	-12.6 (7.9)	83.7 (7.7)	-10.9 (7.1)	82.9 (8.5)	-11.7 (7.5)
Median	83.0	-13.0	84.0	-12.0	83.0	-12.0
Min–max	51.0–100.0	-28.0 to 3.0	65.0–100.0	-31.0 to 6.0	51.0–100.0	-31.0 to 6.0
Week 20						
Pre-walk						
N	110		102		213	
Mean (SD)	94.5 (4.2)		94.0 (4.9)		94.3 (4.5)	
Median	95.0		95.0		95.0	
Min–max	74.0–100.0		74.0–100.0		74.0–100.0	
During walk						
N	105	105	99	99	205	205
Mean (SD)	76.2 (8.9)	-18.2 (8.4)	74.5 (11.8)	-19.4 (11.8)	75.4 (10.4)	-18.7 (10.2)
Median	77.0	-17.0	76.0	-17.0	76.0	-17.0
Min–max	42.0–95.0	-54.0 to 4.0	0.0–95.0	-97.0 to -3.0	0.0–95.0	-97.0 to 4.0
Post-walk						
n	109	109	102	102	212	212
Mean (SD)	82.3 (9.8)	-12.2 (9.3)	81.1 (9.1)	-12.9 (8.4)	81.7 (9.4)	-12.5 (8.8)
Median	82.0	-12.0	81.0	-13.0	81.0	-13.0

Min–max	42.0–100.0	-54.0 to 5.0	55.0–100.0	-39.0 to 4.0	42.0–100.0	-54.0 to 5.0
Week 28						
Pre-walk						
N	100		89		190	
Mean (SD)	94.6 (4.2)		93.5 (4.4)		94.1 (4.3)	
Median	95.0		94.0		95.0	
Min–max	81.0–100.0		80.0–100.0		80.0–100.0	
During walk						
N	99	99	86	86	186	186
Mean (SD)	76.2 (9.8)	-18.4 (10.0)	75.0 (11.5)	-18.4 (11.1)	75.7 (10.6)	-18.3 (10.5)
Median	75.0	-18.0	76.0	-18.0	75.0	-18.0
Min–max	23.0–95.0	-75.0 to 0.0	0.0–95.0	-91.0 to 0.0	0.0–95.0	-91.0 to 0.0
Post-walk						
N	100	100	89	89	190	190
Mean (SD)	82.0 (9.3)	-12.6 (9.1)	81.3 (8.3)	-12.2 (7.9)	81.7 (8.8)	-12.4 (8.5)
Median	82.5	-12.5	81.0	-13.0	82.0	-13.0
Min–max	57.0–100.0	-35.0 to 3.0	63.0–99.0	-27.0 to 9.0	57.0–100.0	-35.0 to 9.0
Week 40						

Pre-walk						
n	79		62		141	
Mean (SD)	94.3 (5.8)		92.0 (12.9)		93.3 (9.6)	
Median	95.0		94.0		95.0	
Min–max	67.0–100.0		0.0–100.0		0.0–100.0	
During walk						
n	72	72	59	59	131	131
Mean (SD)	77.8 (8.8)	-16.8 (8.7)	75.1 (13.7)	-16.9 (19.9)	76.6 (11.3)	-16.8 (14.8)
Median	79.0	-16.0	77.0	-16.0	77.0	-16.0
Min–max	43.0–98.0	-55.0 to -2.0	0.0–96.0	-91.0 to 93.0	0.0–98.0	-91.0 to 93.0
Post-walk						
n	76	76	62	62	138	138
Mean (SD)	83.6 (8.6)	-11.0 (8.3)	80.8 (8.8)	-11.2 (16.2)	82.4 (8.8)	-11.1 (12.4)
Median	84.0	-12.0	80.5	-13.5	82.0	-12.0
Min–max	64.0–100.0	-32.0 to 11.0	58.0–99.0	-37.0 to 95.0	58.0–100.0	-37.0 to 95.0
Week 52						
Pre-walk						
n	68		55		124	

Mean (SD)	95.0 (4.3)		94.3 (4.9)		94.7 (4.6)	
Median	96.0		96.0		96.0	
Min–max	77.0–100.0		80.0–100.0		77.0–100.0	
During walk						
N	66	66	51	51	118	118
Mean (SD)	76.9 (10.3)	-18.0 (9.3)	74.7 (9.0)	-19.6 (9.8)	75.9 (9.7)	-18.7 (9.5)
Median	78.0	-17.0	75.0	-19.0	77.0	-17.0
Min–max	38.0–95.0	-62.0 to -3.0	54.0–95.0	-44.0 to -2.0	38.0–95.0	-62.0 to -2.0
Post-walk						
n	68	68	55	55	124	124
Mean (SD)	82.4 (11.3)	-12.6 (10.3)	82.0 (9.1)	-12.3 (8.3)	82.2 (10.3)	-12.5 (9.3)
Median	83.0	-13.0	83.0	-12.0	83.0	-12.5
Min–max	41.0–114.0	-36.0 to 22.0	63.0–100.0	-33.0 to 3.0	41.0–114.0	-36.0 to 22.0
Week 64						
Pre-walk						
N	67		42		110	
Mean (SD)	95.5 (3.9)		94.6 (4.3)		95.1 (4.1)	
Median	96.0		95.0		96.0	

Min–max	75.0–100.0		83.0–100.0		75.0–100.0	
During walk						
n	63	63	40	40	104	104
Mean (SD)	77.3 (8.6)	-18.4 (7.8)	76.9 (9.4)	-17.7 (7.1)	77.1 (8.9)	-18.1 (7.5)
Median	78.0	-18.0	78.0	-18.5	78.0	-18.0
Min–max	41.0–93.0	-46.0 to -2.0	56.0–93.0	-31.0 to -3.0	41.0–93.0	-46.0 to -2.0
Post-walk						
N	67	67	41	41	109	109
Mean (SD)	83.6 (9.8)	-11.9 (8.8)	83.7 (9.1)	-11.0 (7.5)	83.6 (9.4)	-11.6 (8.3)
Median	83.0	-12.0	84.0	-11.0	84.0	-12.0
Min–max	60.0–99.0	-31.0 to 3.0	61.0–98.0	-24.0 to 4.0	60.0–99.0	-31.0 to 4.0

Sp02: blood oxygen saturation; RCT: randomised controlled trial; OLE: open-label extension; SD: standard deviation; min: minimum; max: maximum.

[a]Week 16 reflects the baseline of the OLE. Baseline data from the RCT have been previously published [3].

Table S5. Supplemental Oxygen Use (L/min)

Visit Time Point Value	Received Inhaled Treprostinil in INCREASE RCT (n=119)		Received Placebo in INCREASE RCT (n=121)		All OLE Patients (N=242)	
	Value	Change from Week 16[a]	Value	Change from Week 16[a]	Value	Change from Week 16[a]
Week 16[a]						
Pre-walk						
N	86		91		178	
Mean (SD)	4.2 (1.8)		3.9 (1.9)		4.1 (1.9)	
Median	4.0		3.0		4.0	
Min–max	1–10		2–10		1–10	
During walk						
n	94		95		190	
Mean (SD)	6.0 (3.5)		5.5 (3.2)		5.7 (3.4)	
Median	6.0		4.0		5.0	
Min–max	2–25		1–15		1–25	
Week 20						
Pre-walk						

n	85	85	82	82	167	167
Mean (SD)	4.0 (1.7)	0.0 (1.1)	4.2 (2.7)	0.4 (1.5)	4.1 (2.3)	0.2 (1.3)
Median	4.0	0.0	4.0	0.0	4.0	0.0
Min–max	2–10	-6 to 3	2–15	-4 to 9	2–15	-6 to 9
During walk						
n	89	85	84	79	173	164
Mean (SD)	5.9 (3.3)	0.0 (0.7)	5.3 (3.1)	0.1 (0.6)	5.6 (3.2)	0.1 (0.7)
Median	6.0	0.0	4.0	0.0	5.0	0.0
Min–max	2–25	-5 to 3	1–15	-2 to 3	1–25	-5 to 3
Week 28						
Pre-walk						
n	74	74	74	74	148	148
Mean (SD)	4.5 (2.1)	0.3 (1.4)	4.2 (2.3)	0.5 (1.5)	4.4 (2.2)	0.4 (1.5)
Median	4.0	0.0	4.0	0.0	4.0	0.0
Min–max	2–12	-5 to 7	2–15	-4 to 5	2–15	-5 to 7
During walk						
n	82	78	71	68	153	146
Mean (SD)	6.4 (3.6)	0.3 (1.3)	5.4 (3.1)	0.3 (0.8)	5.9 (3.4)	0.3 (1.1)

Median	6.0	0.0	4.0	0.0	6.0	0.0
Min–max	2–25	-5 to 6	2–15	0–3	2–25	-5 to 6
Week 40						
Pre-walk						
n	63	63	54	54	118	118
Mean (SD)	4.6 (2.3)	0.8 (1.8)	3.8 (1.8)	0.3 (1.4)	4.3 (2.1)	0.6 (1.6)
Median	4.0	0.0	3.5	0.0	4.0	0.0
Min–max	2–15	-2 to 7	2–10	-4 to 5	2–15	-4 to 7
During walk						
n	60	55	52	48	112	103
Mean (SD)	6.0 (2.8)	0.3 (1.0)	5.3 (3.1)	0.3 (0.9)	5.6 (2.9)	0.3 (1.0)
Median	6.0	0.0	4.0	0.0	5.0	0.0
Min–max	2–15	0–5	2–15	0–4	2–15	0–5
Week 52						
Pre-walk						
n	52	52	44	44	96	96
Mean (SD)	4.1 (1.5)	0.3 (1.7)	4.2 (2.5)	1.0 (2.2)	4.2 (2.0)	0.6 (2.0)
Median	4.0	0.0	3.5	0.0	4.0	0.0

Min–max	2–8	-6 to 4	2–15	-1 to 13	2–15	-6 to 13
During walk						
n	52	47	47	43	99	90
Mean (SD)	6.0 (2.4)	0.0 (1.0)	5.2 (2.7)	0.6 (1.6)	5.6 (2.6)	0.3 (1.3)
Median	6.0	0.0	4.0	0.0	6.0	0.0
Min–max	2–15	-5 to 3	2–15	0–9	2–15	-5 to 9
Week 64						
Pre-walk						
n	50	50	33	33	83	83
Mean (SD)	4.2 (1.8)	0.5 (2.0)	3.7 (1.8)	0.5 (1.5)	4.0 (1.8)	0.5 (1.8)
Median	4.0	0.0	3.0	0.0	4.0	0.0
Min–max	2–10	-6 to 7	1–10	-4 to 6	1–10	-6 to 7
During walk						
n	52	49	34	31	86	80
Mean (SD)	6.0 (2.8)	0.3 (1.9)	5.3 (3.1)	0.8 (1.9)	5.7 (2.9)	0.5 (1.9)
Median	6.0	0.0	4.0	0.0	6.0	0.0
Min–max	2–15	-7 to 9	2–15	-1 to 9	2–15	-7 to 9

RCT: randomised controlled trial; OLE: open-label extension; SD: standard deviation; min: minimum; max: maximum. [a]For the patients previously on inhaled treprostinil in the parent RCT, baseline refers to week 0 of the INCREASE RCT. For patients previously on placebo in the parent RCT, baseline refers to their first dose of inhaled treprostinil taken in the OLE.

[a]Week 16 reflects the baseline of the OLE. Baseline data from the RCT have been previously published [3].

Figure S1. Median Dose of Inhaled Treprostinil Achieved in INCREASE Open-Label Extension (OLE). RCT: randomised controlled trial.

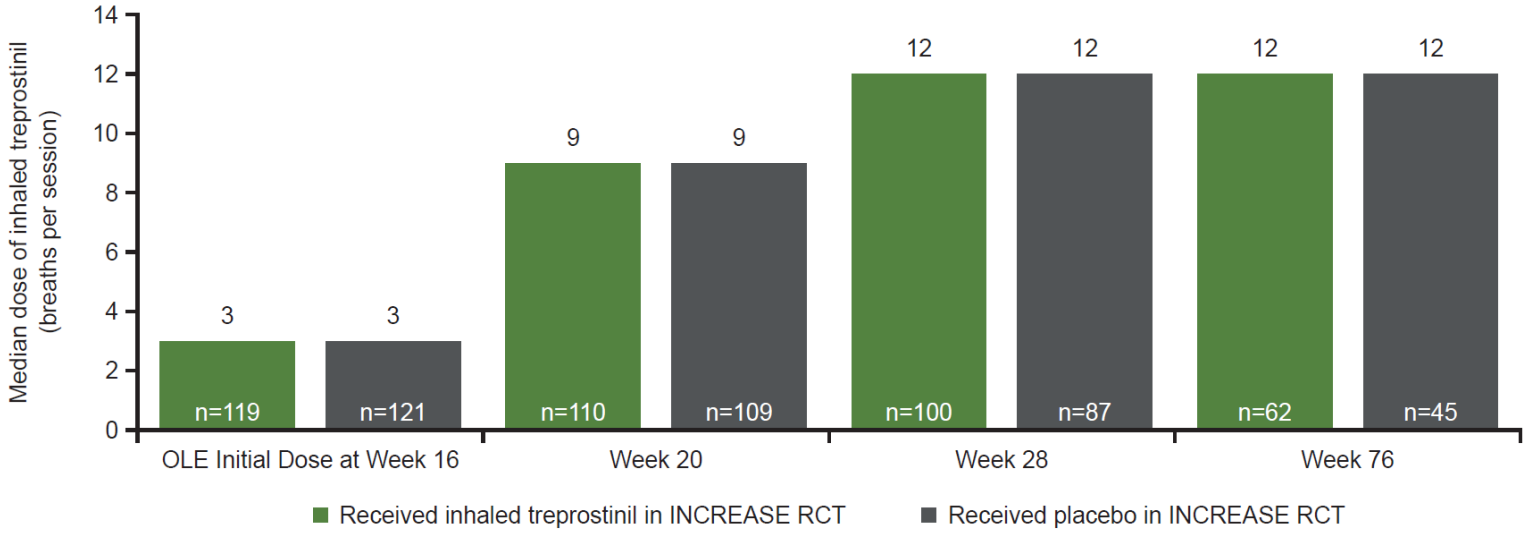
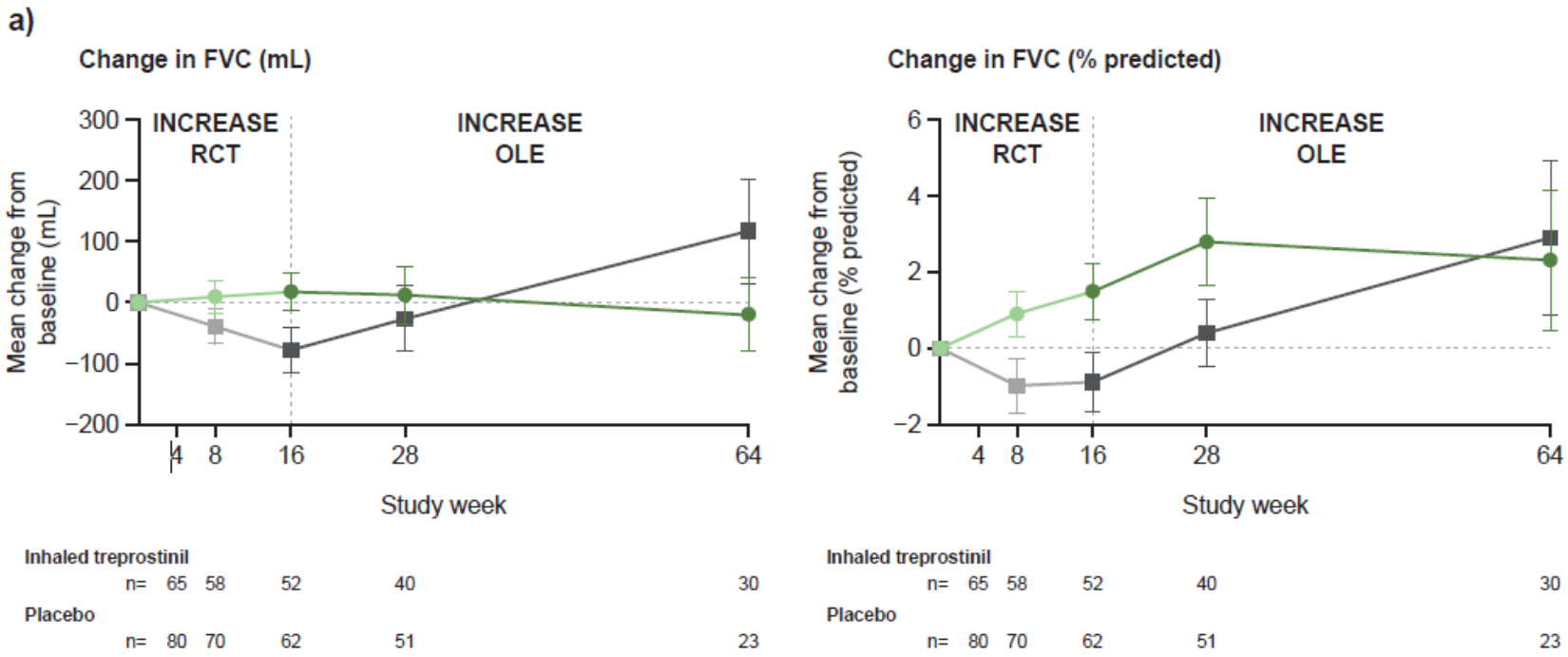
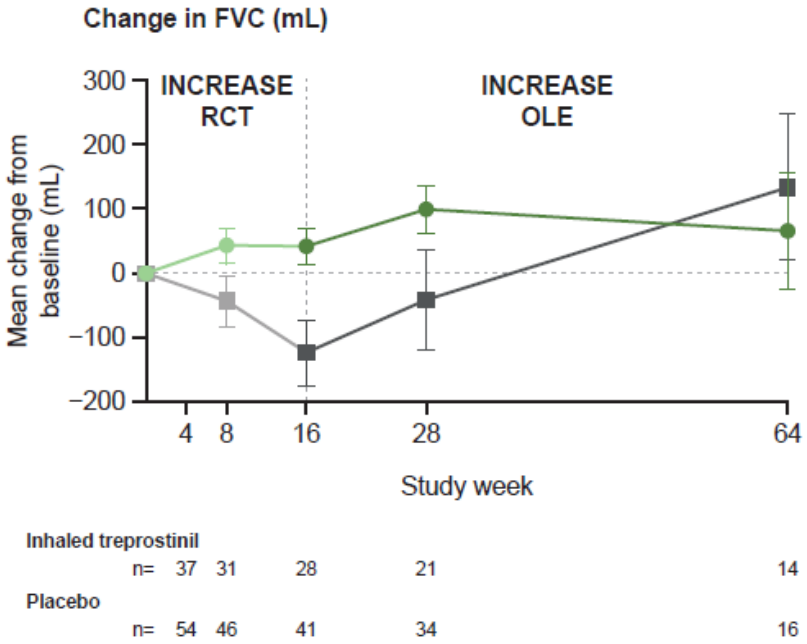


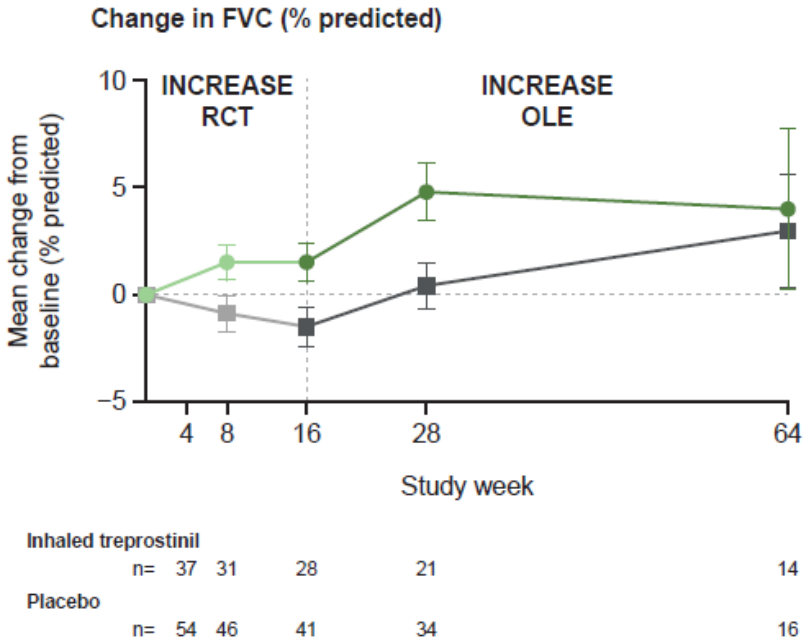
Figure S2. Change in FVC by Lung Disease Subtype

Change in forced vital capacity (FVC) in mL and percent predicted for a) idiopathic interstitial pneumonia, including idiopathic pulmonary fibrosis, b) idiopathic pulmonary fibrosis alone, c) combined pulmonary fibrosis and emphysema, and d) connective tissue disease. RCT: randomised controlled trial; OLE: open-label extension. All available data at each time point are included in the figure.

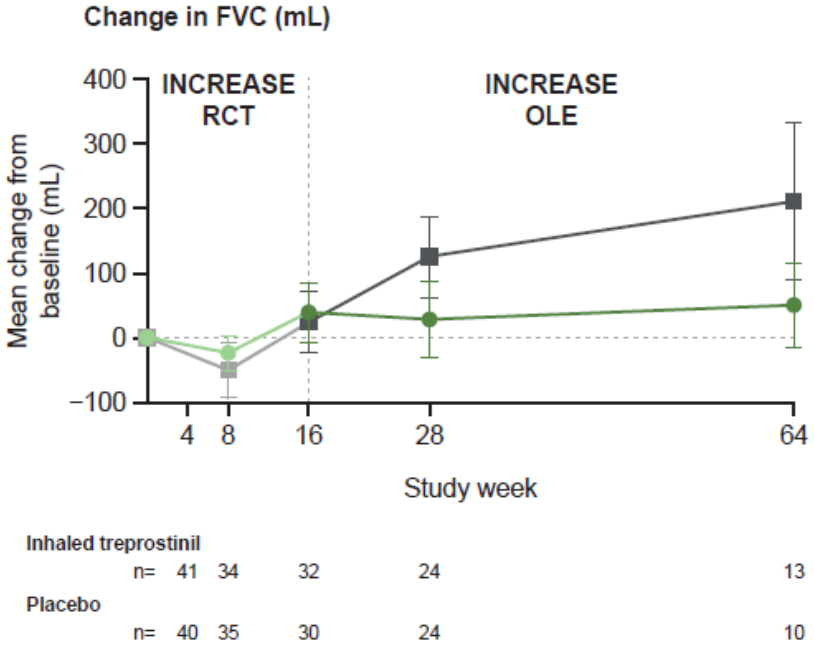


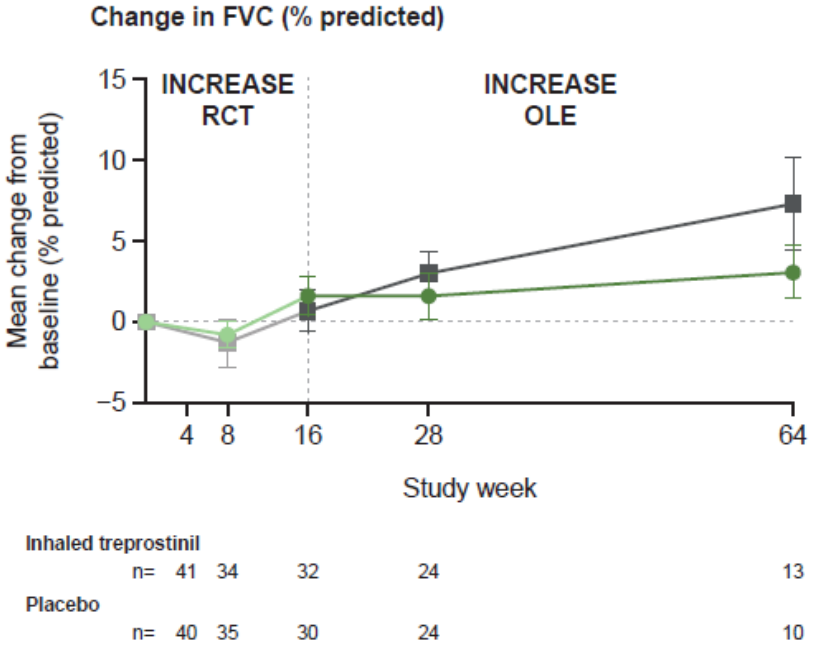
b)


Change in FVC (mL)
INCREASE RCT
INCREASE OLE
Mean change from baseline (mL)
300
200
100
0
−100
−200
4
8
16
28
64
Study week
Inhaled treprostinil
n= 37 31 28 21 14
Placebo
n= 54 46 41 34 16

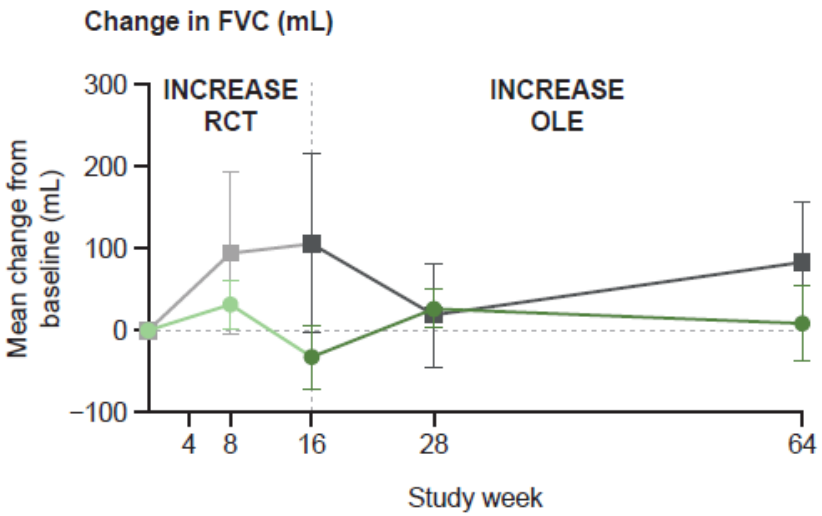

Change in FVC (% predicted)
INCREASE RCT
INCREASE OLE
Mean change from baseline (% predicted)
10
5
0
−5
4
8
16
28
64
Study week
Inhaled treprostinil
n= 37 31 28 21 14
Placebo
n= 54 46 41 34 16

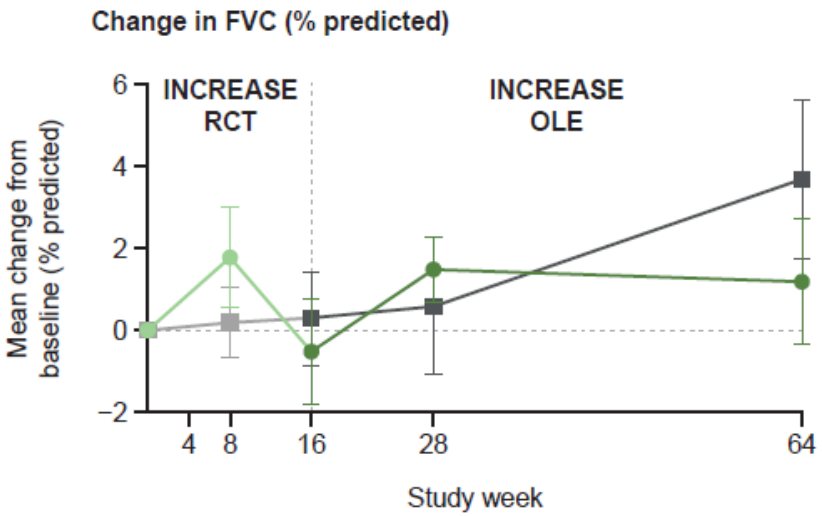
c)


Change in FVC (mL)
INCREASE RCT
INCREASE OLE
Mean change from baseline (mL)
400
300
200
100
0
−100
4
8
16
28
64
Study week
Inhaled treprostinil
n= 41 34 32 24 13
Placebo
n= 40 35 30 24 10


Change in FVC (% predicted)
INCREASE RCT
INCREASE OLE
Mean change from baseline (% predicted)
15
10
5
0
−5
4
8
16
28
64
Study week
Inhaled treprostinil
n= 41 34 32 24 13
Placebo
n= 40 35 30 24 10

d)


Change in FVC (mL)
INCREASE RCT
INCREASE OLE
Mean change from baseline (mL)
300
200
100
0
−100
4
8
16
28
64
Study week
Inhaled treprostinil
n= 40 37 34 27 17
Placebo
n= 31 26 24 17 11


Change in FVC (% predicted)
INCREASE RCT
INCREASE OLE
Mean change from baseline (% predicted)
6
4
2
0
−2
4
8
16
28
64
Study week
Inhaled treprostinil
n= 40 37 34 27 17
Placebo
n= 31 26 24 17 11

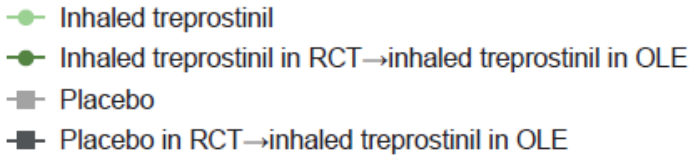

Inhaled treprostinil
Inhaled treprostinil in RCT→inhaled treprostinil in OLE
Placebo
Placebo in RCT→inhaled treprostinil in OLE

Figure S3. Time to Cardiopulmonary Hospitalization

Kaplan-Meier estimates of time to hospitalization due to cardiopulmonary indication from the INCREASE open-label extension (OLE) baseline (week 16) in all patients. [a]Hazard ratio (HR), 95% confidence interval (CI), and p-value were calculated from a Cox proportional hazards model with the parent study treatment group as an explanatory variable.

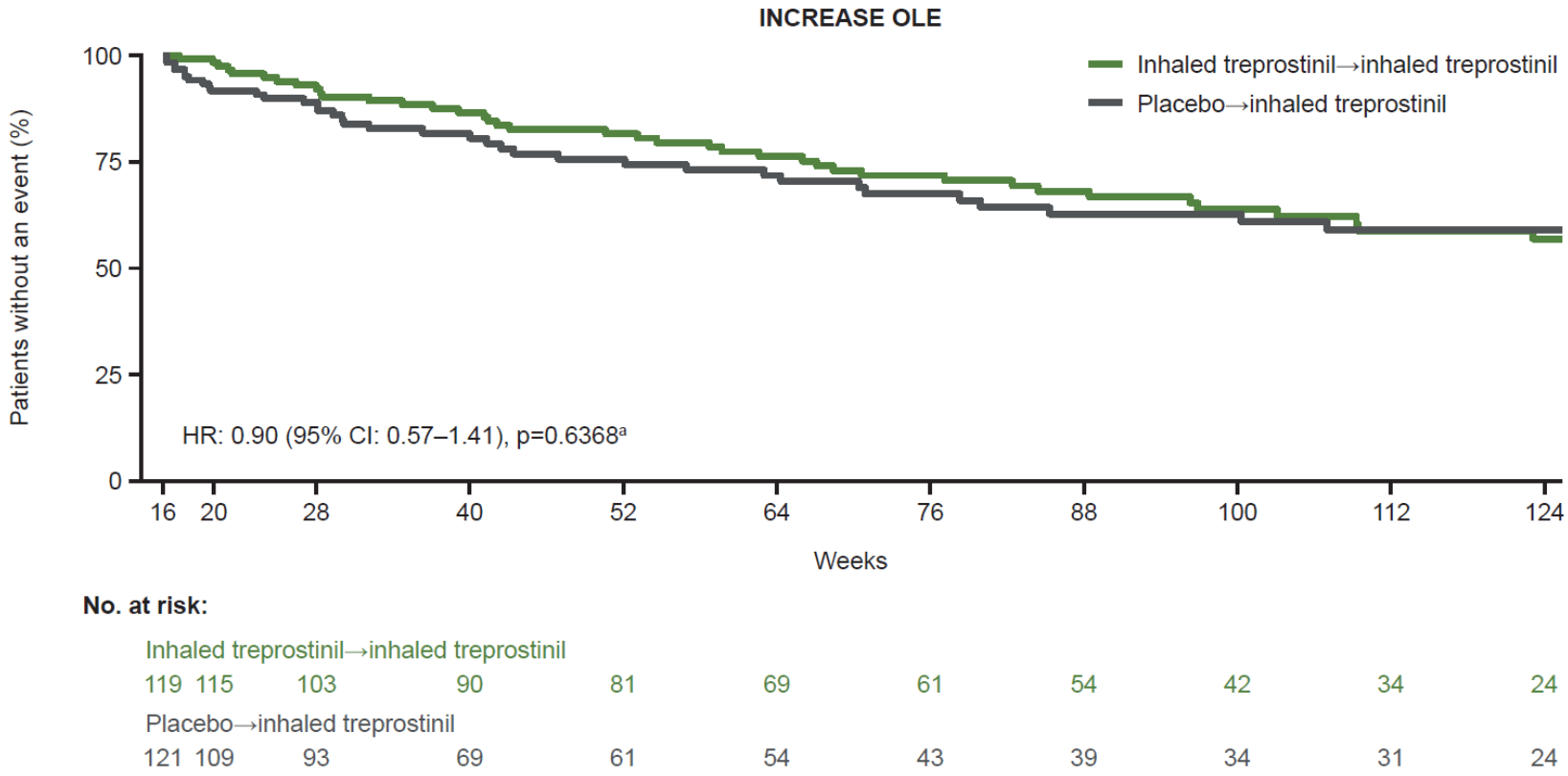
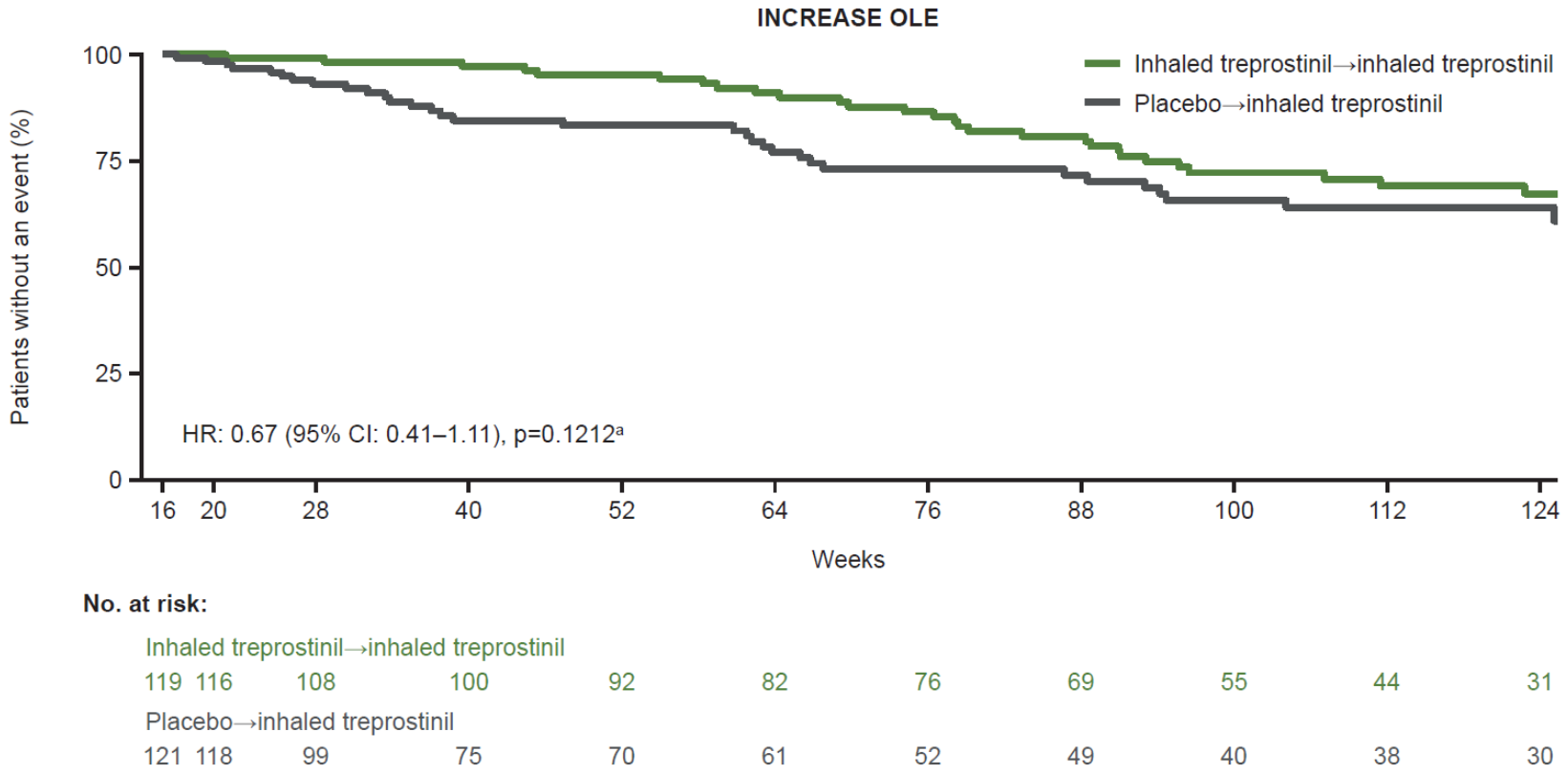


Figure S4. Time to Death

Kaplan-Meier estimates of time to death from the INCREASE open-label extension (OLE) baseline (week 16) in all patients. [a]Hazard ratio (HR), 95% confidence interval (CI), and p-value were calculated from a Cox proportional hazards model with the parent study treatment group as an explanatory variable.



REFERENCES

1 Welling JB, Hartman JE, Ten Hacken NH, *et al*. The minimal important difference for the St George's Respiratory Questionnaire in patients with severe COPD. *Eur Respir J* 2015; 46: 1598–1604.

2 Lettieri CJ, Nathan SD, Browning RF, *et al*. The distance-saturation product predicts mortality in idiopathic pulmonary fibrosis. *Respir Med* 2006; 100: 1734–1741.

3 Waxman A, Restrepo-Jaramillo R, Thenappan T, *et al*. Inhaled treprostinil in pulmonary hypertension due to interstitial lung disease. *N Engl J Med* 2021; 384: 325–334.

Long-term Inhaled Treprostinil for PH-ILD:INCREASE Open-Label Extension Study

INCREASE-OLE: Open-label extension of INCREASE, a 16-week, randomised, double-blind, placebo-controlled, phase 3 trial

242 patients with PH-ILD enrolled in INCREASE-OLE and received inhaled treprostinil

Key Long-term Assessments (Efficacy and Safety)

- 6MWD
- AEs
- FVC
- NT-proBNP
- Exacerbation of lung disease

6MWD

3.5 m
median change at wk 52*

279.1 m
Mean 6MWD at wk 52

Data for overall population

Exacerbation of lung disease

31% Lower relative risk

for patients who received inhaled treprostinil versus placebo in RCT

HR=0.69 (95% CI: 0.49-0.97); *P*=0.03

NT-proBNP

Baseline* **389** pg/ml

Wk 64 **359** pg/ml

Median values in overall population

Safety

Overall profile was consistent with RCT: most common AEs were cough (27%), dyspnoea (26%), and headache (19%). No new safety signals were observed. AEs led to drug discontinuation in 22% of patients.

Change in FVC

+51 mL Absolute

+2.8% % predicted

Mean change at wk 64* for overall population

**From RCT baseline (wk 0).*
6MWD, 6-minute walk distance; AE, adverse event; CI, confidence interval; FVC, forced vital capacity; HR, hazard ratio; NT-proBNP, N-terminal pro-brain natriuretic peptide; OLE, open-label extension; PH-ILD, pulmonary hypertension due to interstitial lung disease; RCT, randomised controlled trial.

The INCREASE-OLE supports the safety and efficacy of long-term treatment with inhaled treprostinil in patients with PH-ILD