United Therapeutics CORPORATION

# TYVASO INCREASE TRIAL RESULTS

*January 2021*

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# AGENDA

| | |
|---|---|
| Introduction | **DEWEY STEADMAN**<br>Head of Investor Relations, United Therapeutics Corporation |
| INCREASE Trial Results | **STEVEN D. NATHAN, MD**<br>INCREASE Study Investigator<br>Director of the Advanced Lung Disease Program and Director of the Lung Transplant Program at Inova Fairfax Hospital, Falls Church, VA |
| INCREASE Commercial Plan | **MICHAEL BENKOWITZ**<br>President and Chief Operating Officer, United Therapeutics Corporation |
| Q&A | **DEWEY STEADMAN**<br>Head of Investor Relations, UTC<br><br>**MICHAEL BENKOWITZ**<br>President and COO, UTC<br><br>**STEVEN D. NATHAN, MD**<br>INCREASE Study Investigator<br><br>**JAMES EDGEMOND**<br>CFO and Treasurer, UTC<br><br>**LEIGH PETERSON, PhD**<br>Vice President, Product Development, UTC |

# STEVEN D. NATHAN, MD

## Steven D. Nathan, MD

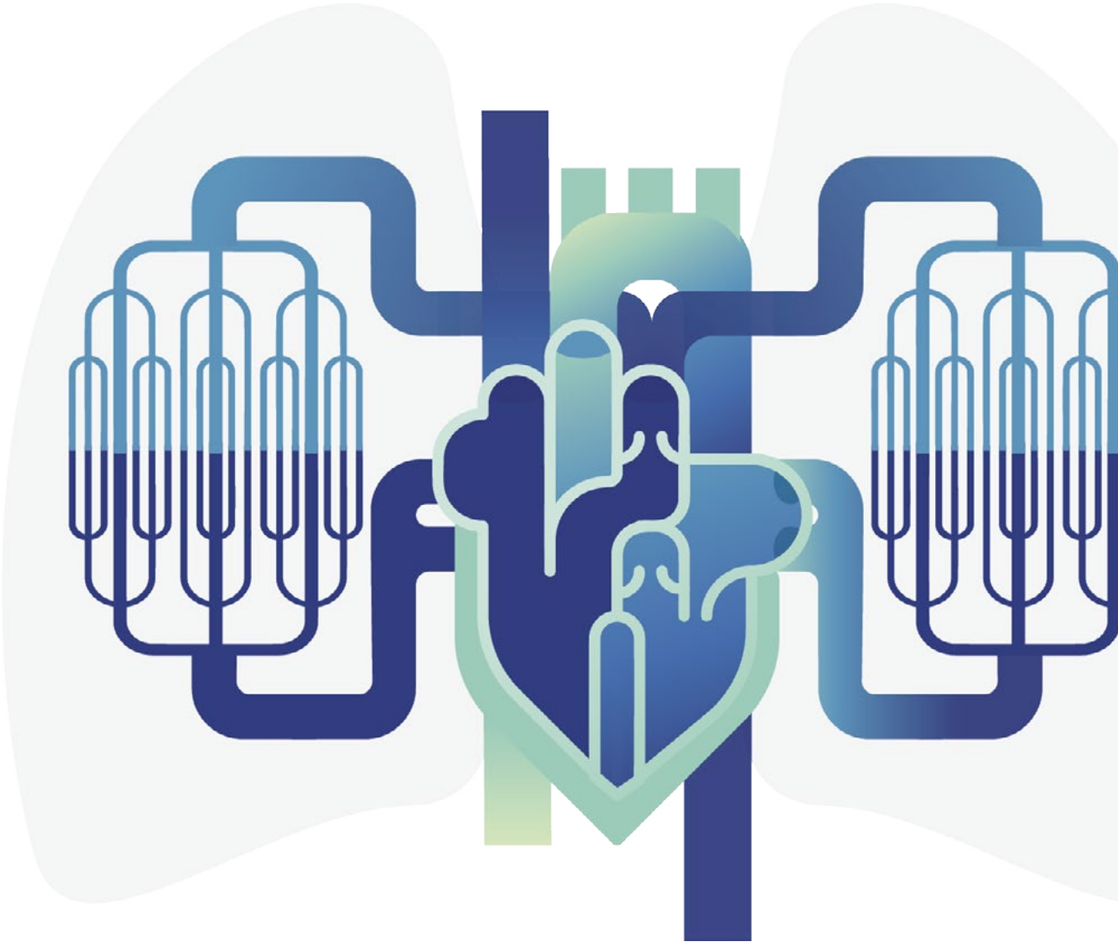
Steven D. Nathan, MD, FCCP, is director of the Advanced Lung Disease Program and director of the Lung Transplant Program at Inova Fairfax Hospital. He also is professor of medicine at Virginia Commonwealth University Inova Campus.

Dr. Nathan is board certified in pulmonary diseases, critical care medicine and internal medicine.

The author of more than 380 publications, Dr. Nathan has written original research manuscripts, abstracts, reviews, book chapters, and a book on idiopathic pulmonary fibrosis (IPF), which he co-edited. Dr. Nathan is a reviewer for multiple journals and is on the editorial board for the journal, *Thorax*. He has served on multiple committees, including U.S. Food and Drug Administration advisory boards as well as steering committees for clinical trials in IPF and pulmonary hypertension, where he has also served as chair. He is also chairperson of Pilot for IPF, an international educational initiative for pulmonary fibrosis.

Dr. Nathan is a member of several professional medical associations, including the American Thoracic Society, the American College of Chest Physicians, and the International Society for Heart and Lung Transplantation. He has delivered talks and been chairperson of numerous sessions at many national and international conferences.

# Background



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# WSPH Classification of Pulmonary Hypertension

**Pulmonary Hypertension***

Resting mean pulmonary artery pressure (mPAP) >20 mmHg with an accompanying pulmonary vascular resistance (PVR) ≥3 Wood Units on right heart catheterization (RHC)[1]

**Group 1**
Pulmonary Arterial Hypertension (PAH)

**Group 2**
Pulmonary Hypertension due to Left Heart Disease

**Group 3**
**Pulmonary Hypertension due to Lung Disease and/or Hypoxia**

**Group 4**
Pulmonary Hypertension due to Pulmonary Artery Obstructions

**Group 5**
Pulmonary Hypertension with Unclear and/or Multifactorial Mechanisms

**Pulmonary Hypertension due to Interstitial Lung Disease (PH-ILD)**

**Pulmonary hypertension associated with fibrotic lung disease, other than sarcoidosis[2]**

Pulmonary Hypertension due to:
- Chronic obstructive pulmonary disease (PH-COPD)
- Diseases with mixed restrictive and obstructive pattern
- Chronic high-altitude exposure
- Sleep disordered breathing
- Alveolar hypoventilation disorders
- Developmental lung diseases

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* Proposed definition from 6th World Symposium on Pulmonary Hypertension

1. Simonneau G, Montani D, Celermajer DS, et al. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. Eur Respir J 2019; 53:; pii: 1801913. 2. King CS, Nathan SD. Pulmonary hypertension due to interstitial lung disease. Curr Opin Pulm Med. 2019 Sep;25(5):459-467.

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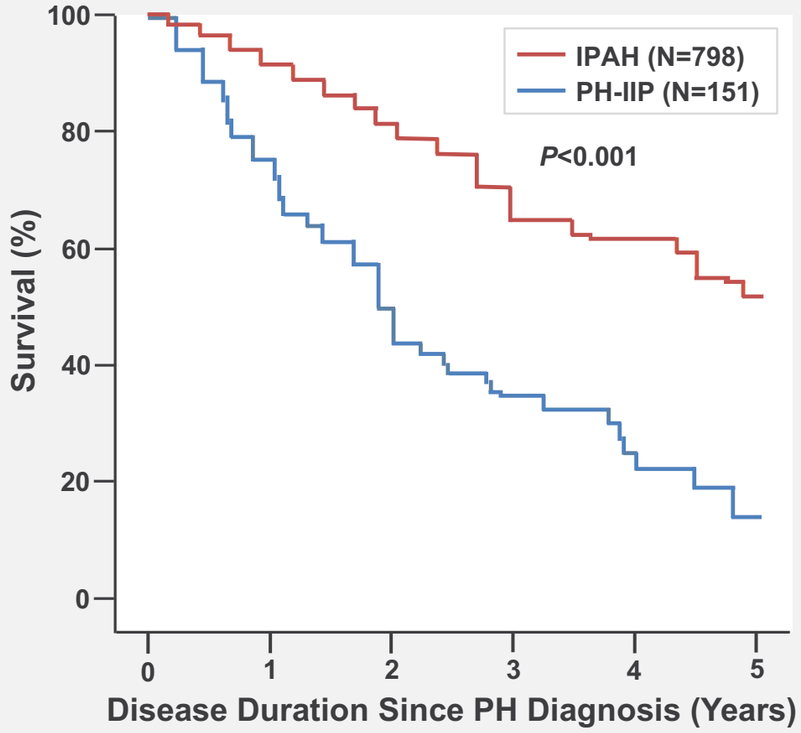
# Pulmonary Hypertension due to Interstitial Lung Disease (PH-ILD)

- Interstitial lung disease (ILD) encompasses a heterogeneous group of parenchymal lung diseases.
- PH-ILD is associated with poor prognosis, worsened functional status, decreased quality of life, increased need for supplemental oxygen, and markedly reduced survival.[1,2]

Kaplan-Meier Survival Estimates in Patients with PH Associated with Chronic Fibrosing Idiopathic Interstitial Pneumonias and Idiopathic PAH – Data from the COMPERA Registry[3]




IIP: idiopathic interstitial pneumonias; ILD: interstitial lung disease; IPAH: idiopathic pulmonary arterial hypertension; PH: pulmonary hypertension.

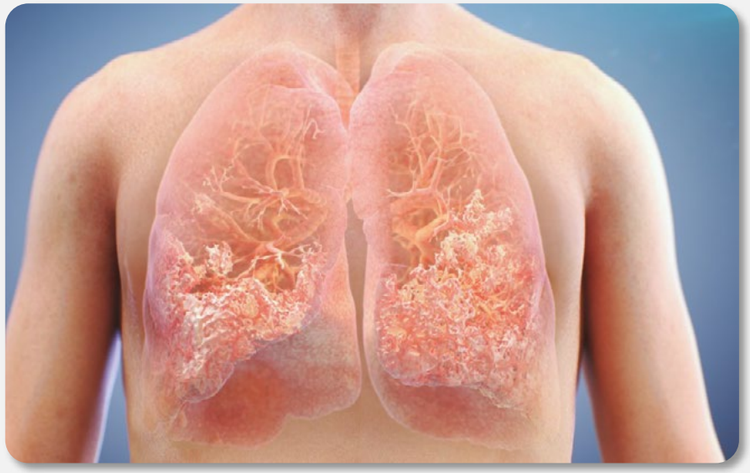
1. Nathan SD. Int J Clin Pract. 2008;62(Suppl 160):21-28. 2. Nathan SD, Hassoun PM. Clin Chest Med. 2013;34(4):695-705. 3. Hoeper MM, Behr J, Held M, et al. PLOS ONE. 2015; 10(12): e0141911.

# Epidemiology of PH-ILD

- Prevalence of ILD (US population-based study):[1]

| Annually | Annually |
|---|---|
| 80.9 cases per 100,000 | 67.2 cases per 100,000 |
| 31.5 new cases per 100,000 | 26.1 new cases per 100,000 |

- Precise prevalence of PH in patients with ILD is difficult to establish.
  - Most of the studies are from case reports and retrospective series.
  - Annual incidence of idiopathic pulmonary fibrosis (IPF) estimated as 6.8 – 8.8 cases per 100,000 population using narrow case definitions.
  - 16.3 – 17.4 cases per 100,000 population using broad case definitions.
- In early stages of the disease or at diagnosis, up to 15% of ILD patients already have PH.[2]
  - As ILD advances, frequency of PH continues to rise, beyond 50%.[3]



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ILD: interstitial lung disease; PH: pulmonary hypertension.

1. Coultas DB, Zumwalt RE, Black WC, et al. Am J Respir Crit Care Med 1994;150:967–972. 2. Collum S.D., Amione-Guerra J., Cruz-Solbes A.-S., et al. Can Respir J. 2017;2017:1430350. 3. Shorr A.F., Wainwright J.L., Cors C.S., et al. Eur Respir J. 2007;30:715–721.

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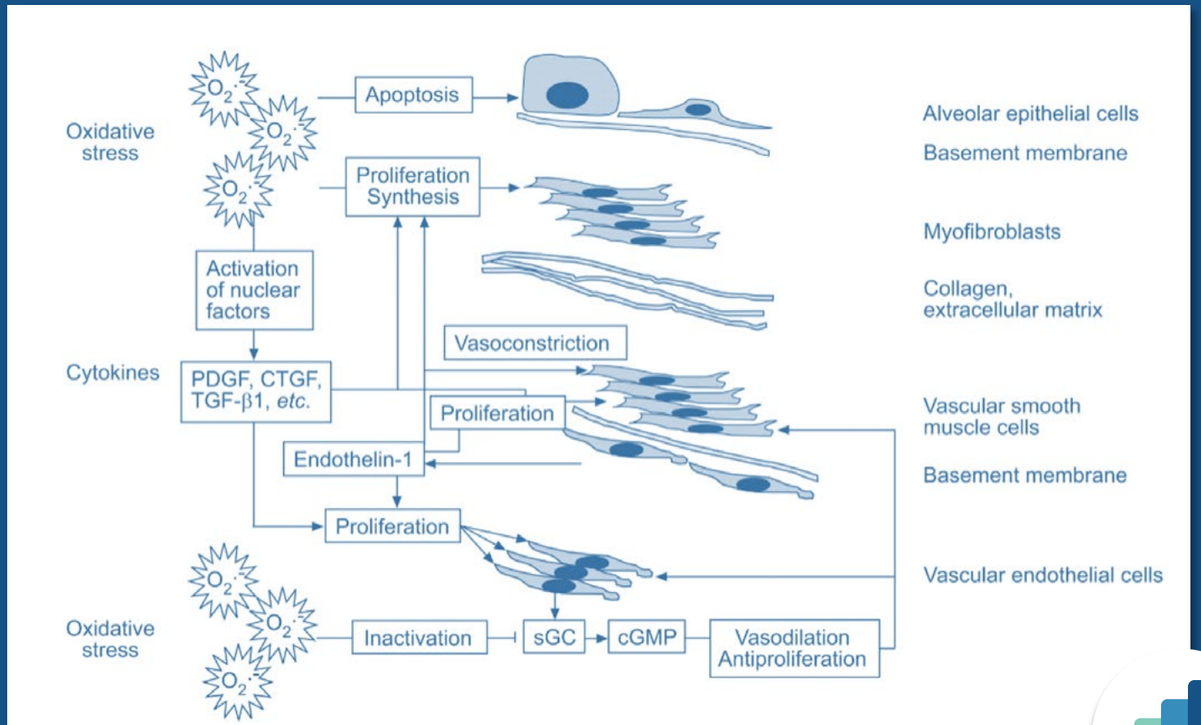
# Pathophysiology of PH-ILD

- The mechanisms underlying the development of PH-ILD are complex, overlapping, and incompletely understood.[1]
- Various factors contribute to PH development, including:[2]
  - Hypoxemia
  - Vascular remodeling
  - Fibrogenesis
  - Disruptions in normal angiogenesis
- All of these factors lead to decreased quantity of pulmonary vessels, impaired ability to vasodilate resulting in increased PVR.

**Potential Mechanisms of Remodeling in ILD and PH[3]**




ILD: interstitial lung disease; PH: pulmonary hypertension; PVR: pulmonary vascular resistance.

1. Klinger JR. Cardiol Clin 2016; 34:413–433. 2. King CS, Nathan SD. Curr Opin Pulm Med. 2019 Sep;25(5):459-467. 3 Behr J, Ryu JH. Eur Respir J. 2008 Jun;31(6):1357-67.

# PH-ILD Study Outcomes

## Previous clinical trials have not conclusively demonstrated efficacy for pulmonary vasodilator therapy in PH-ILD

| Proposed Treatment | Results |
|---|---|
| SILDENAFIL | STEP-IPF study did not achieve 20% change in 6MWD, but did suggest increased quality of life and decreased shortness of breath[1] |
| BOSENTAN | BUILD-1, -2, -3 failed to improve 6MWD[2,3] and the time to occurrence of lung fibrosis worsening[4] B-PHIT showed no improvement in hemodynamics, functional class, or symptoms[5] |
| MACITENTAN | MUSIC study found no significant difference in PFTs, time to disease worsening, or death[6] |
| AMBRISENTAN | ARTEMIS-IPF was stopped early due to increased rate of disease progression and respiratory hospitalizations; **use contraindicated** |
| RIOCIGUAT | RISE-IIP study terminated due to risk of death and other serious adverse events as compared to placebo; **use contraindicated** |

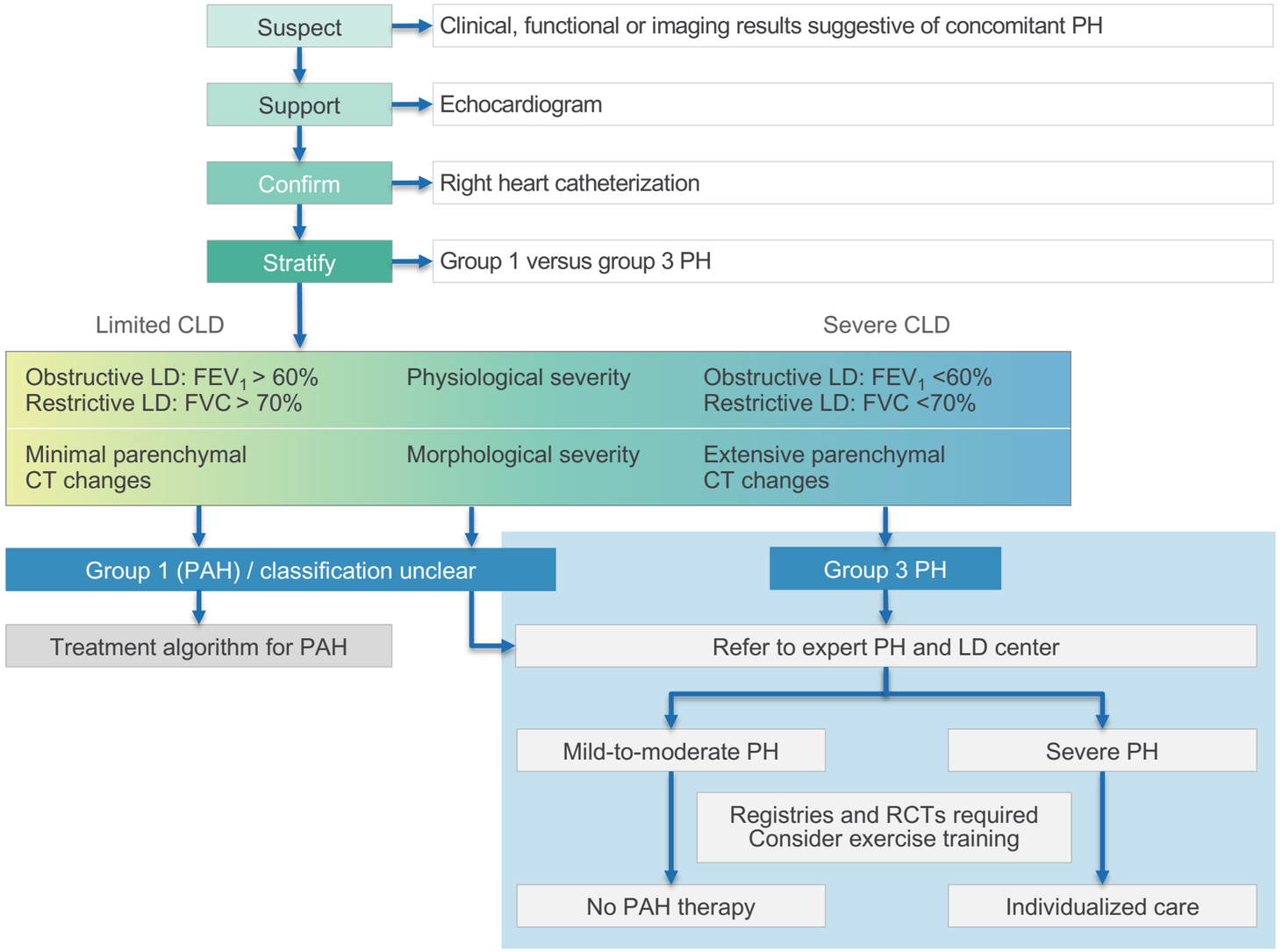
6MWD: six-minute walk distance; ILD: interstitial lung disease; PFT: pulmonary function tests; PH: pulmonary hypertension.

1. The Idiopathic Pulmonary Fibrosis Clinical Research Network, et al. N Engl J Med. 2010;363(7):620-628. 2. King TE Jr, et al. Am J Respir Crit Care Med. 2008;177(1):75-81. 3. Seibold JR, et al. Arthritis Rheum. 2010;62(7):2101-2108. 4. King TE Jr, et al. Am J Respir Crit Care med. 2011;184(1):92-99. 5. Corte TJ, et al. Am J Respir Crit Care Med. 2014;190(2):208-217. 6. Raghu G, et al. Eur Respir J. 2013;42(6):1622-1632.

# Current Management and Treatment Considerations

There are currently no approved therapies for PH-ILD.

In a survey study of 30 pulmonary vascular disease centers, 80% reported using PAH therapy in Group 3 PH.[1]




CLD: chronic lung disease; CT: computed tomography; FEV1: forced expiratory volume in 1 second; FVC: forced vital capacity; ILD: interstitial lung disease; LD: lung disease; PAH: pulmonary arterial hypertension; PH: pulmonary hypertension; RCT: randomized controlled trial.

1. Trammell AW, Pugh ME, Newman JH, et al. Pulm Circ 2015;5(2):356-63. 2. Nathan et al. Eur Respir J 2019; 53: 1801914

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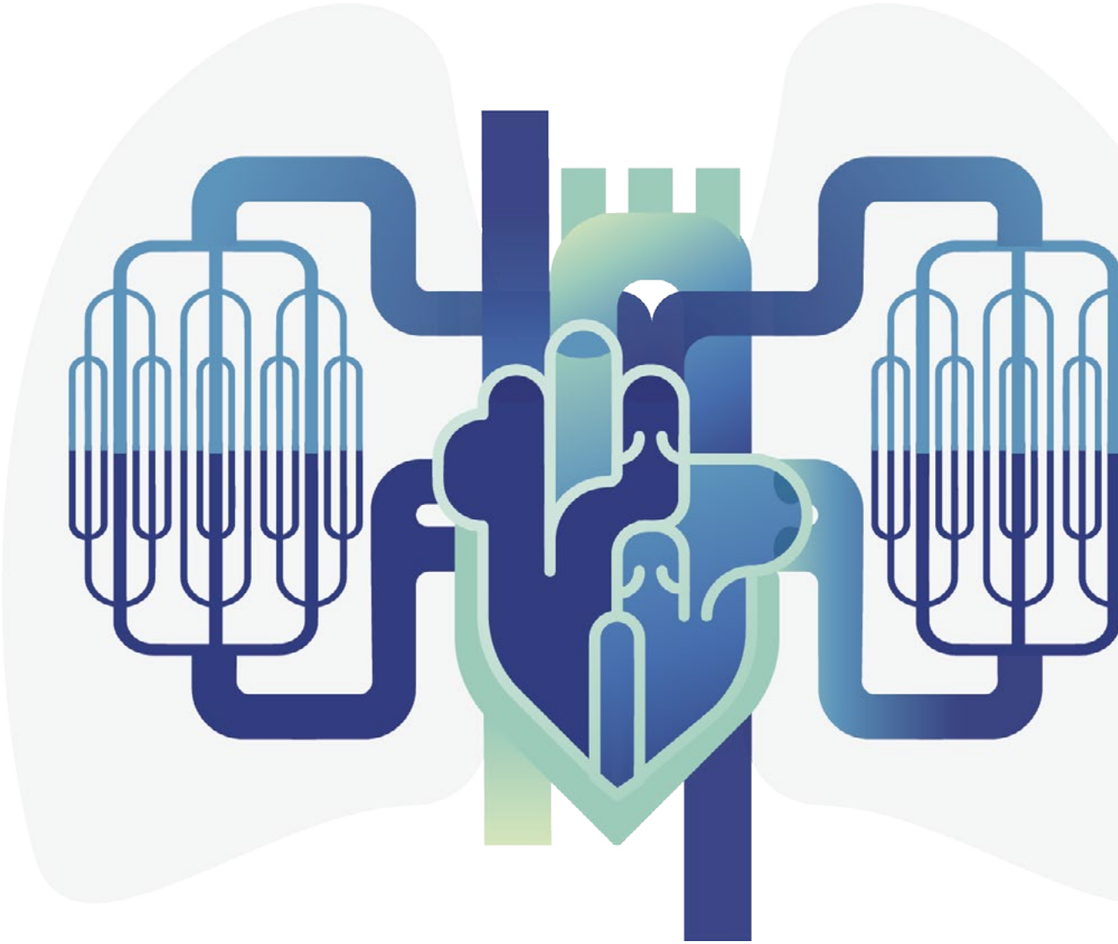
A Multicenter, Randomized, Double-Blinded, Placebo-Controlled Trial to Evaluate the Safety and Efficacy of Inhaled Treprostinil in Patients with Pulmonary Hypertension due to Interstitial Lung Disease



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# INCREASE – Study Design and Inclusion Criteria

Phase 3, multicenter, randomized (1:1), double-blind, placebo-controlled, 16-week, parallel-group (inhaled treprostinil / placebo) study (NCT02630316)

## Key Inclusion Criteria

- Confirmed diagnosis of Group 3 PH based on CT within 6 months prior to randomization and demonstrated evidence of diffuse parenchymal lung disease. Subjects had any form of ILD or CPFE
- Right heart catheterization within 1 year prior to randomization with the following documented parameters:
  - **PVR >3 WU and**
  - **PCWP ≤15 mmHg and**
  - **mPAP ≥25 mmHg**
- Baseline 6MWD ≥100 m
- Subjects on a chronic medication for underlying lung disease (i.e., pirfenidone, nintedanib, etc.) were on a stable and optimized dose for ≥30 days prior to randomization
- Subjects with Group 3 connective tissue disease had a Baseline forced vital capacity <70%

## Key Exclusion Criteria

- Diagnosis of PAH or PH for reasons other than Group 3 PH-ILD
- Use of any PAH-approved therapy, including: prostacyclin therapy, IP receptor agonist, endothelin receptor antagonist, phosphodiesterase type 5 inhibitor, or soluble guanylate cyclase stimulator within 60 days of randomization (or during the study)
- Evidence of clinically significant left-sided heart disease as defined by:
  - **PCWP >15 mmHg**
  - **Left ventricular ejection fraction <40%**
- Receiving >10 L/min of oxygen supplementation by any mode of delivery at rest at Baseline
- Initiation of pulmonary rehabilitation within 12 weeks prior to randomization
- Acute pulmonary embolism within 90 days of randomization

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6MWD: six-minute walk distance; CPFE: combined pulmonary fibrosis and emphysema; CT: computed tomography; mPAP: mean pulmonary arterial pressure; PAH: pulmonary arterial hypertension; PCWP: pulmonary capillary wedge pressure; PH: pulmonary hypertension; PVR: pulmonary vascular resistance.

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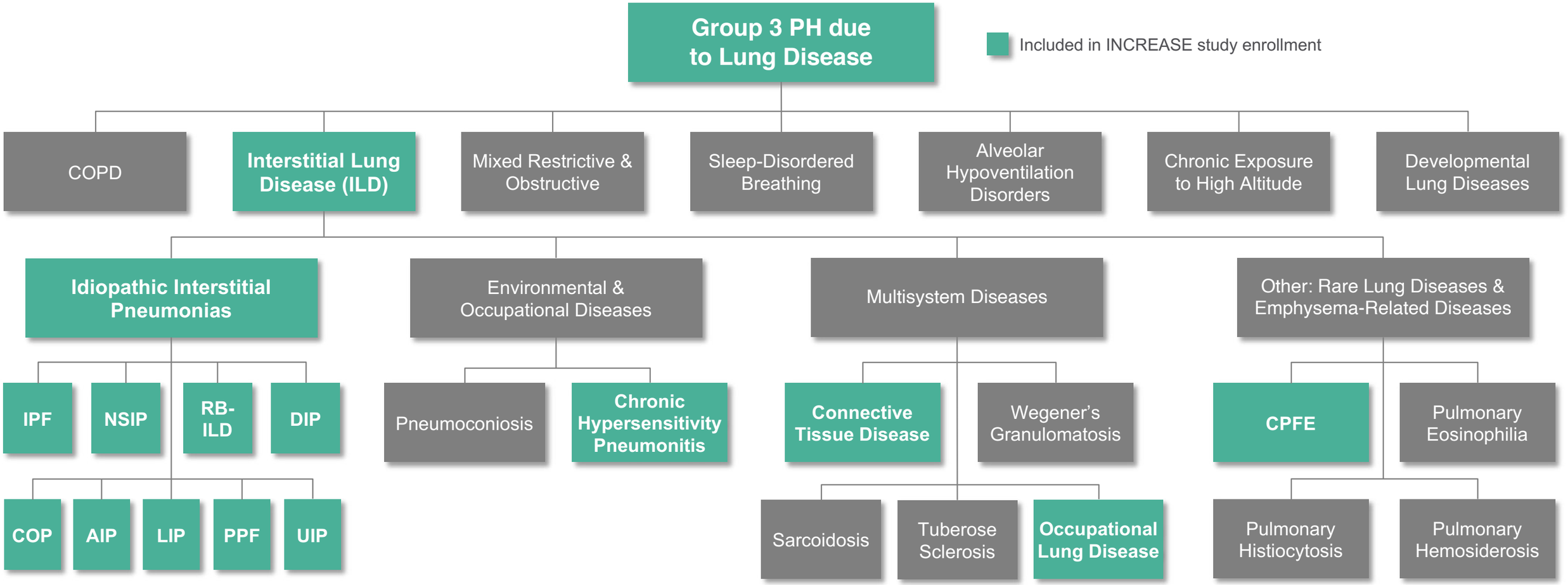
# INCREASE Eligible Study Population




AIP: Acute interstitial pneumonitis; COP: Cryptogenic organizing pneumonia; CPFE: Combined pulmonary fibrosis and emphysema; DIP: Desquamative interstitial pneumonia; IPF: Idiopathic Pulmonary Fibrosis; LIP: Lymphoid Interstitial pneumonia; NSIP: Nonspecific interstitial pneumonia; PPF: Pleuroparenchymal fibroelastosis; RB-ILD: Respiratory bronchiolitis-associated interstitial lung disease; UIP: Unclassifiable interstitial pneumonia.

1. Simonneau G, et al. J Am Coll Cardiol. 2013;62(25):D34-41. 2. Bourke SJ. Postgrad Med J. 2006;82:494-499. 3. "Interstitial Lung Disease" www.erswhitebook.com – accessed December 2015.

# Study Assessments

## Primary Endpoint

- Change in 6MWD measured at peak exposure from Baseline to Week 16
  - 6-minute walk test (6MWT) performed at peak plasma treprostinil exposure
    - Between 10 to 60 minutes after most recent dose of study drug

## Secondary Endpoints

- Change in NT-proBNP from Baseline to Week 16
- Time to clinical worsening - time of randomization until study discontinuation
  - Hospitalization due to a cardiopulmonary indication,
  - Decrease in 6MWD >15% from Baseline directly related to disease under study at 2 consecutive visits and at least 24 hours apart,
  - Death (all causes),
  - Or lung transplantation
- Change in Peak 6MWD at Week 12
- Change in Trough 6MWD at Week 15
  - ≥4 hours after the most recent study drug dose and ≥24 hours prior to Week 16 6MWT

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6MWD: six-minute walk distance; 6MWT: six-minute walk test; NT-proBNP: N-terminal pro-brain natriuretic peptide.

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# Study Assessments

## Exploratory Endpoints

- Change in Quality of Life (SGRQ)
- Change in peak distance saturation product (DSP)
- Change in peak 6MWD from Baseline to Weeks 4 and 8
- Optional evaluation of change in biomarkers and whole genome sequence at Baseline

## Additional Safety Endpoints

- Adverse events (AEs)
- Supplemental Oxygenation Requirements
- Pulse oximetry
- Changes in pulmonary function tests (PFTs)
- Clinical laboratory parameters
- Vital signs
- Electrocardiograms (ECG)
- Exacerbations of underlying lung disease
  - Defined as an acute, clinically significant, respiratory deterioration characterized by evidence of new widespread alveolar abnormality

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SGRQ: St. George's Respiratory Questionnaire.

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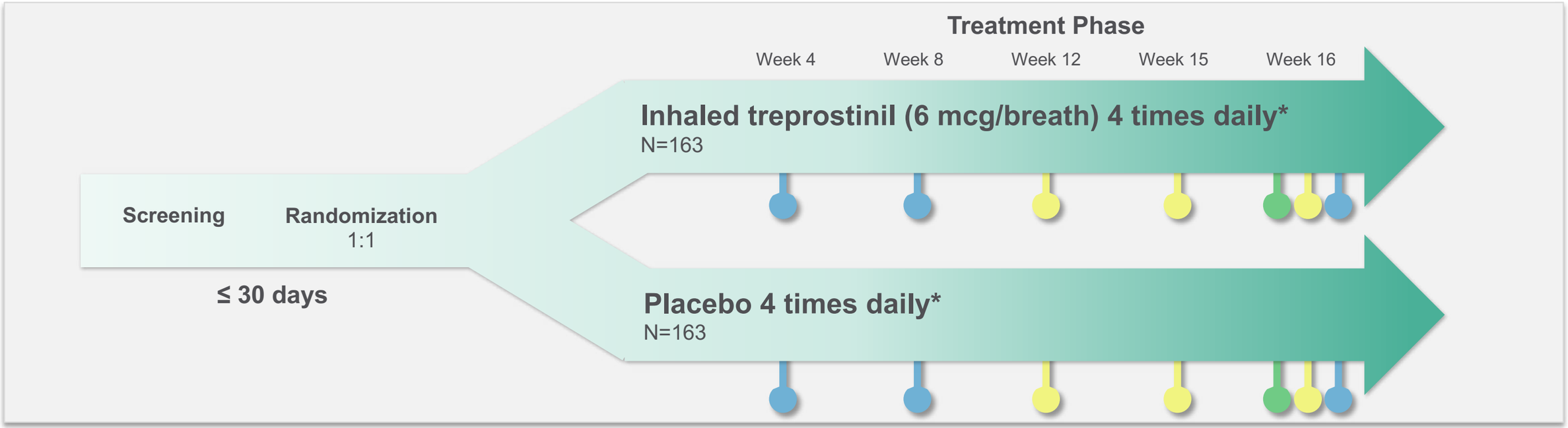
# INCREASE – Study Procedures

## Timeline of Study Endpoint Assessments




* All subjects initiated study drug at a dose of 3 breaths (18 mcg) 4 times daily (during waking hours). Dose escalations (additional 1 breath 4 times daily) could occur up to every 3 days, with a target dose of 9 breaths (54 mcg) 4 times daily and a maximum dose of 12 breaths (72 mcg) 4 times daily, as clinically tolerated.

- Primary endpoint measure - 6MWD at peak exposure from Baseline to Week 16
- Secondary endpoint measures - Change in peak 6MWD Baseline to Week 12; Change in plasma concentration NT-proBNP Baseline to Week 16; Change in trough 6MWD from Baseline to Week 15.
- Exploratory endpoint measures

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6MWD: six-minute walk distance; NT-proBNP: N-terminal pro-brain natriuretic peptide.

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# Baseline Characteristics of Study Population

| | Inhaled Treprostinil N=163 | Placebo N=163 |
|---|---|---|
| **Age** | | |
| Mean (SD) | 65.6 (12.7) | 67.4 (11.2) |
| **Sex, n (%)** | | |
| Male | 78 (47.9%) | 95 (58.3%) |
| Female | 85 (52.1%) | 68 (41.7%) |
| **Time since PH-ILD Diagnosis, years** | | |
| Mean (SD) | 0.54 (1.16) | 0.54 (1.31) |
| **Etiology of PH-ILD, n (%)** | | |
| Idiopathic interstitial pneumonia (IIP) | 65 (39.9%) | 81 (49.7%) |
| *Idiopathic pulmonary fibrosis subtype of IIP* | *37 (22.7%)* | *55 (33.7%)* |
| Combined pulmonary fibrosis and emphysema | 42 (25.8%) | 40 (24.5%) |
| Connective tissue disease | 40 (24.5%) | 32 (19.6%) |
| Chronic hypersensitivity pneumonitis | 10 (6.1%) | 9 (5.5%) |
| Occupational lung disease | 5 (3.1%) | 1 (0.6%) |
| Other | 1 (0.6%) | 0 |
| **Use of Supplemental Oxygen, n (%)** | 119 (73.0%) | 114 (69.9%) |
| **Use of Background Therapy, n (%)** | | |
| None | 133 (81.6%) | 119 (73%) |
| Pirfenidone only | 19 (11.7%) | 25 (15.3%) |
| Nintedanib only | 11 (6.7%) | 19 (11.7%) |

ILD, interstitial lung disease; PH, pulmonary hypertension; SD, standard deviation.

# Baseline Assessments of Study Population

| | TYVASO n=163 | Placebo n=163 |
|---|---|---|
| **6MWD, meters** | | |
| Mean (range) | 254.1 (100-538) | 265.1 (30-505) |
| Median | 256 | 260 |
| **PVR, WU** | | |
| Mean (range) | 6.369 (3.11-18.05) | 6.013 (3.06-17.62) |
| Median | 5.57 | 5.06 |
| **NT-proBNP, pg/mL** | | |
| Mean (range) | 1857.53 (10.2-21942) | 1808.86 (23-16297) |
| Median | 550.5 | 420.8 |
| **mPAP, mm Hg** | | |
| Mean (range) | 37.2 (25-74) | 36 (25-61) |
| Median | 35 | 35 |
| **PCWP, mm Hg** | | |
| Mean (range) | 10.1 (2-20) | 9.6 (0-15) |
| Median | 10 | 10 |

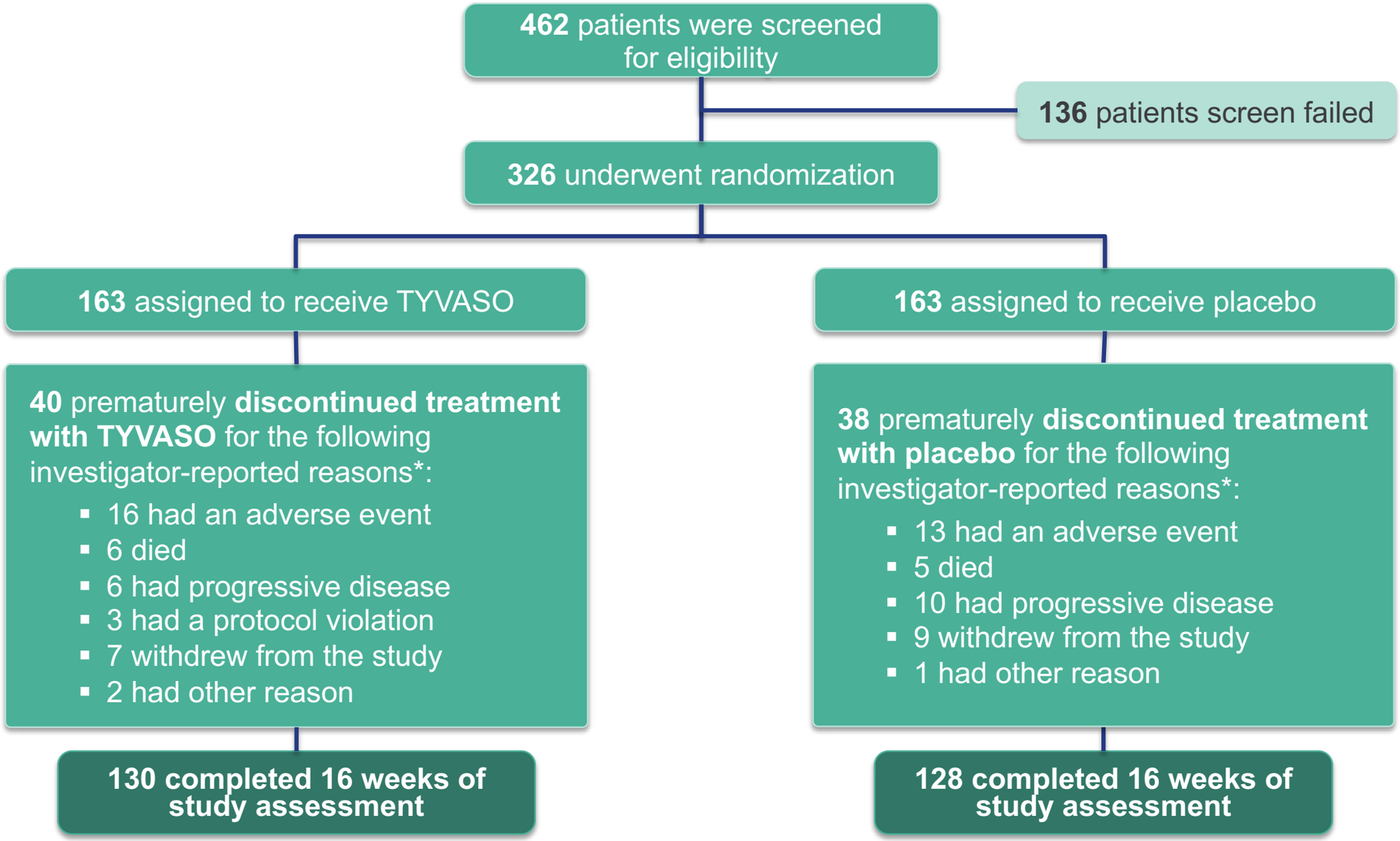
6MWD: 6-minute walk distance; mPAP: mean pulmonary arterial pressure; NT-proBNP: N-terminal pro-brain natriuretic peptide; PCWP: pulmonary capillary wedge pressure; PVR: pulmonary vascular resistance.

# Baseline Assessments of Study Population (Continued)

| Pulmonary Function Tests | Inhaled Treprostinil N=163 | Placebo N=163 |
|---|---|---|
| **$FEV_1$ % Predicted** | | |
| Mean (range) | 63.9 (23, 120) | 65 (22, 145) |
| Median | 63 | 63 |
| **FVC % Predicted** | | |
| Mean (range) | 62.5 (24, 130) | 63.8 (20, 134) |
| Median | 60 | 61 |
| **TLC % Predicted** | | |
| Mean (range) | 62.9 (25, 126) | 64.2 (30, 109) |
| Median | 62 | 62.5 |
| **DLCO % Predicted** | | |
| Mean (range) | 30 (5, 86) | 28.1 (1, 86) |
| Median | 29 | 26 |

DLCO: lung diffusion capacity; FEV1: forced expiratory volume in 1 second; FVC: forced vital capacity; TLC: total lung capacity.

# Screening, Randomization, and Follow-Up




*Patients who discontinued study treatment were not withdrawn but were encouraged to remain in the study and complete assessments through week 16. Overall, 33 patients from the TYVASO arm and 35 from the placebo arm prematurely discontinued study participation.

**Reference:** Data on file. Research Triangle Park, NC: United Therapeutics Corporation; May 2020.

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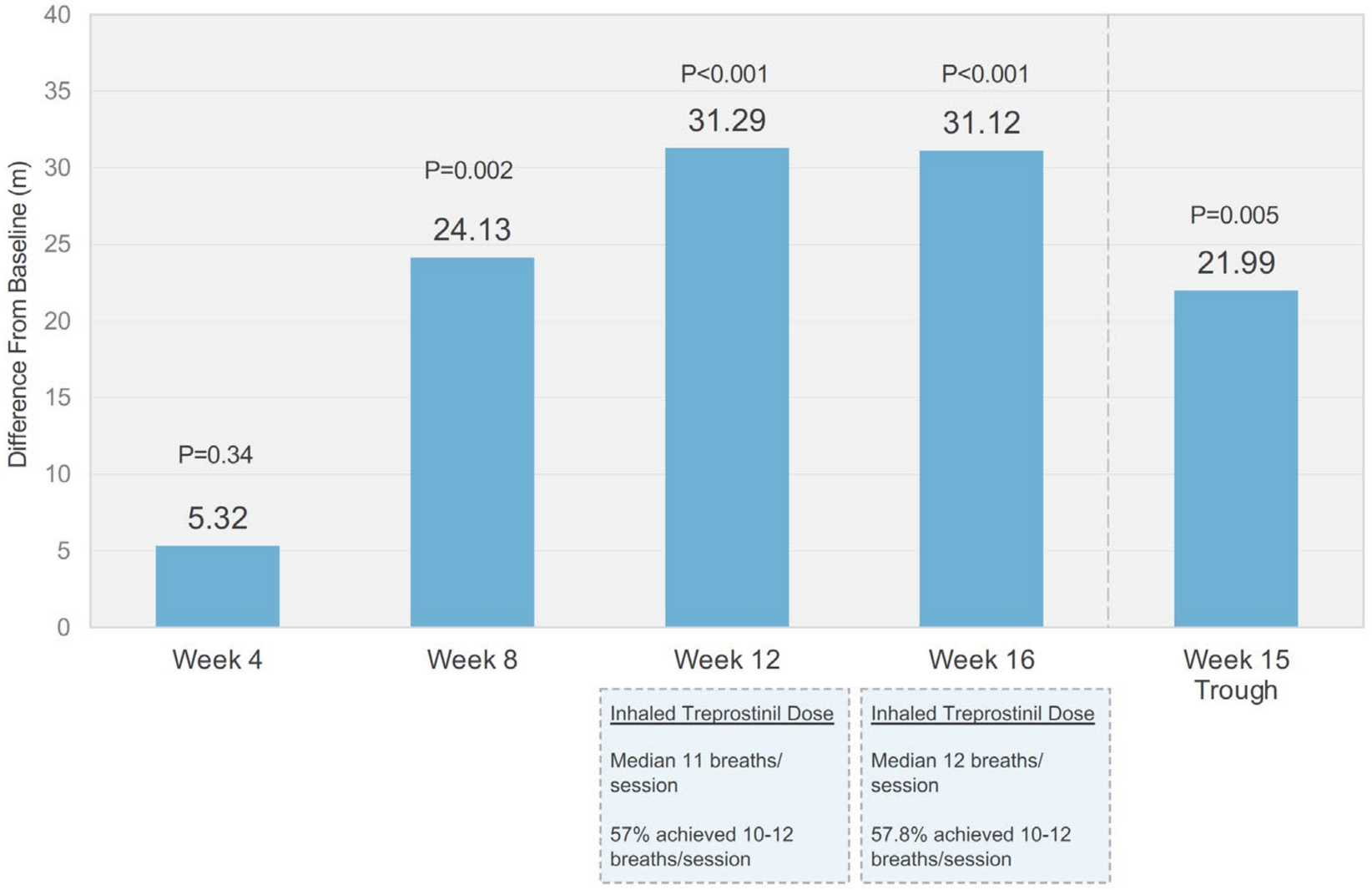
# 6MWD Results Through Week 16 – Mixed Model Repeated Measurement

**At Week 16, inhaled treprostinil patients had a placebo-corrected difference from Baseline in peak 6MWD of 31.12 meters**

**(95% CI: 16.85, 45.39; P<0.001).**




Mixed Model Repeated Measurement treatment effect is provided.
6MWD, 6-Minute Walk Distance; m, meter.

# 6MWD Results Through Week 16

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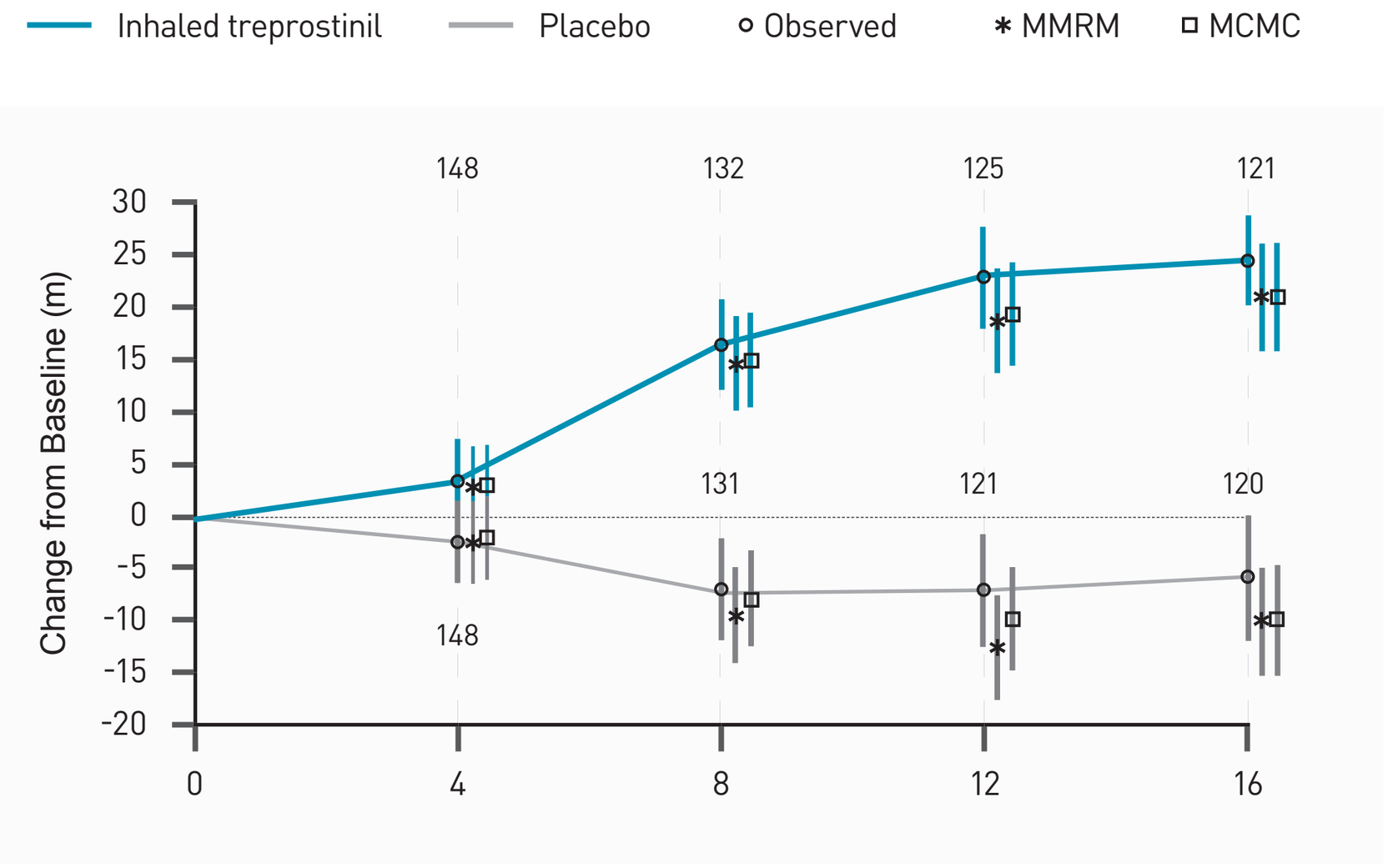
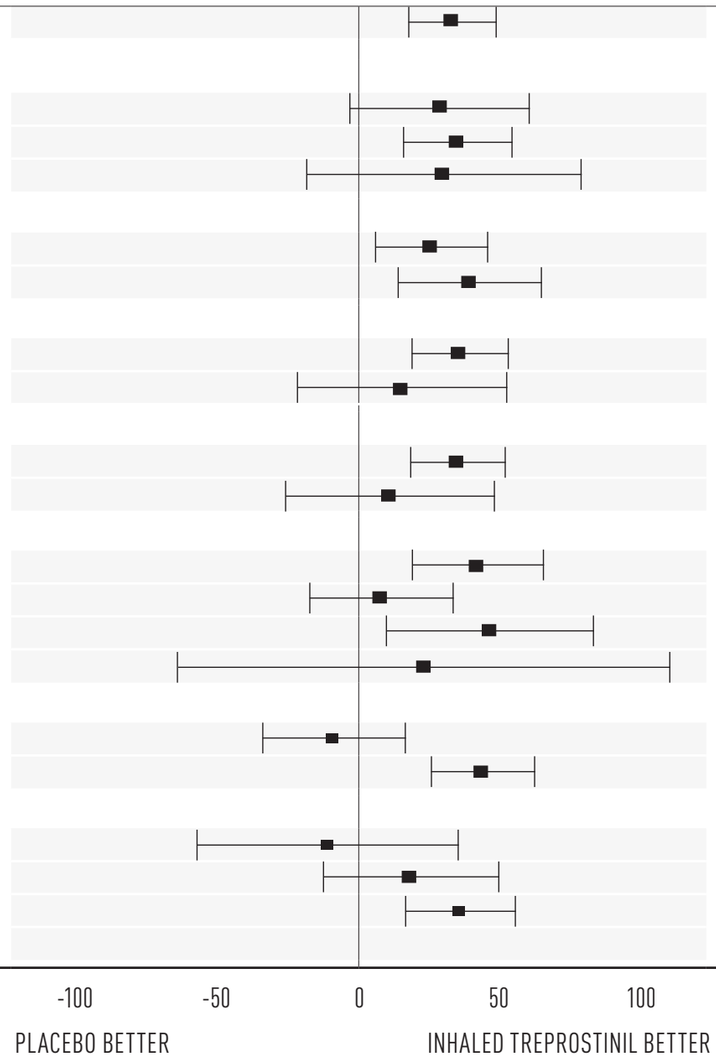



Mixed Model Repeated Measurement treatment effect is provided.
6MWD, 6-Minute Walk Distance; m, meter; MMRM = mixed-model repeat-measurement; MCMC = Markov chain Monte Carlo

# Subgroup Analyses of Peak 6MWD at Week 16 – MMRM Analysis

| SUBGROUP | INHALED TREPROSTINIL # PATIENTS | PLACEBO # PATIENTS | LS MEAN DIFFERENCE (95% CI) |
|---|---|---|---|
| OVERALL | 121 | 120 | 31.1 (16.9, 45.4) |
| AGE GROUP | | | |
| <65 years | 48 | 32 | 27.0 (-2.2, 56.1) |
| 65 to 80 years | 63 | 78 | 32.9 (15.2, 50.5) |
| ≥80 years | 10 | 10 | 28.3 (-16.2, 72.9) |
| SEX | | | |
| Male | 55 | 68 | 24.3 (6.1, 42.5) |
| Female | 66 | 52 | 36.9 (13.7, 60.0) |
| BASELINE 6MWD CATEGORY | | | |
| ≤350 meters | 99 | 100 | 33.8 (18.0, 49.6) |
| >350 meters | 22 | 20 | 14.6 (-19.5, 48.7) |
| BASELINE DLCO (% Predicted) | | | |
| <40% | 90 | 98 | 33.0 (17.7, 48.3) |
| ≥40% | 23 | 18 | 10.7 (-23.5, 45.0) |
| PH-ILD ETIOLOGY | | | |
| Idiopathic Interstitial Pneumonia | 48 | 62 | 39.5 (18.3, 60.7) |
| Combined Pulmonary Fibrosis and Emphysema | 30 | 28 | 7.9 (-15.4, 31.3) |
| Connective Tissue Disease | 34 | 24 | 43.5 (9.6, 77.4) |
| Other | 9 | 6 | 22.4 (-61.4, 106.3) |
| BASELINE PVR CATEGORY | | | |
| <4 Wood units | 27 | 25 | --7.6 (-30.9, 15.6) |
| ≥4 Wood units | 94 | 95 | 40.8 (24.1, 57.6) |
| MAXIMUM STUDY DRUG DOSE | | | |
| 4-6 breaths | 6 | 2 | |
| 7-9 breaths | 37 | 24 | -9.5 (-52.2, 33.1) |
| 10-12 breaths | 77 | 92 | 17.7 (-10.9, 46.2) |
| >12 breaths | 1 | 2 | 33.7 (15.8, 51.7) |




6MWD, 6-minute walk distance; CI, confidence interval; ILD, interstitial lung disease; LOCF, PH, pulmonary hypertension; PVR, pulmonary vascular resistance

# Secondary and Exploratory Endpoints

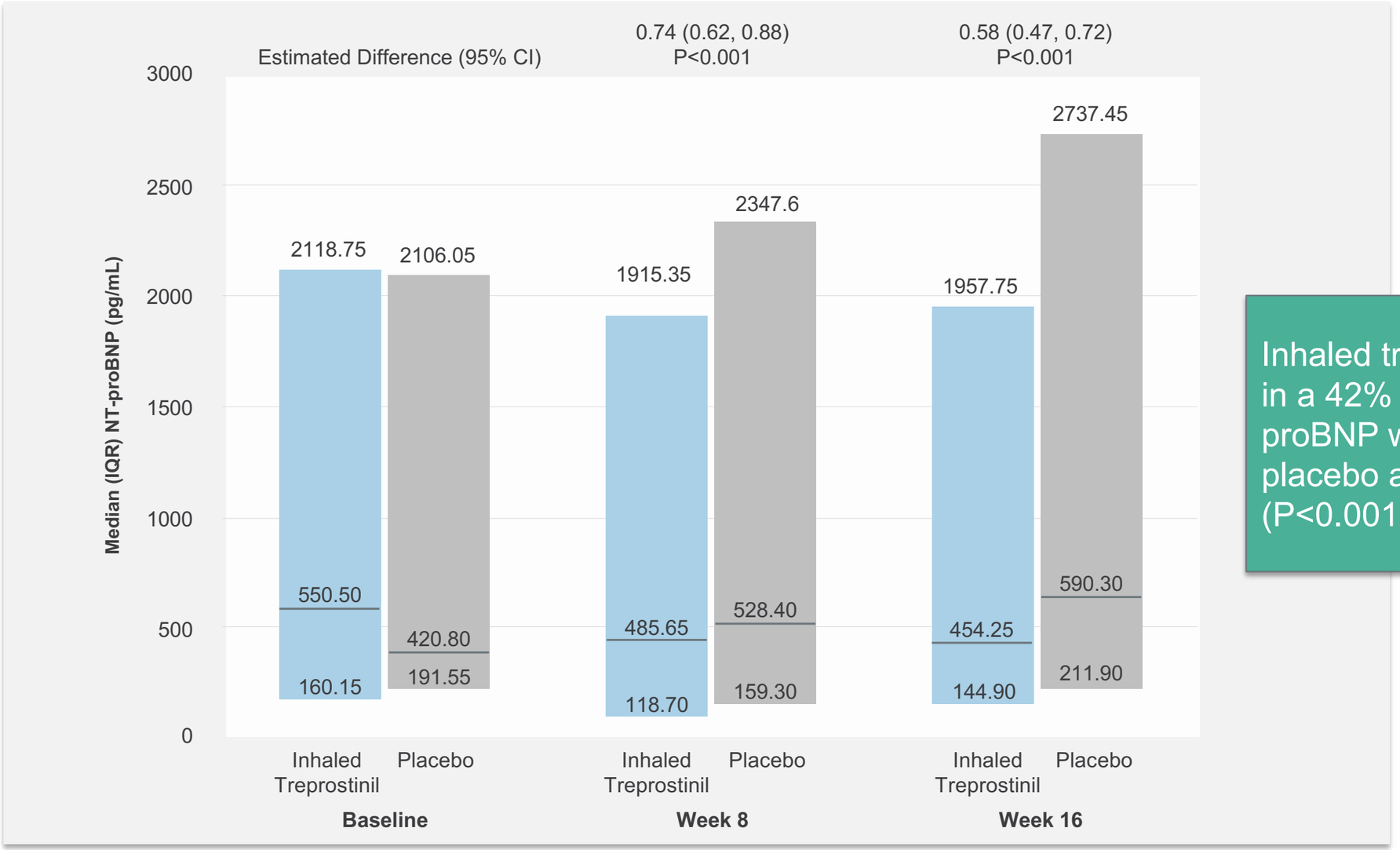
Significant differences were observed with inhaled treprostinil, including:

- Improvements in NT-proBNP
- Reduction in time to clinical worsening
- Improvements in peak 6MWD at Week 12
- Improvements in trough 6MWD at Week 15

No significant differences in patient-reported SGRQ or DSP at Week 16

6MWD: six-minute walk distance; DSP: distance saturation product; NT-proBNP: N-terminal pro-brain natriuretic peptide; SGRQ: The St. George's Respiratory Questionnaire.

# NT-proBNP Results by Study Visit




Inhaled treprostinil resulted in a 42% reduction in NT-proBNP when compared to placebo at Week 16 (P<0.001).

CI: confidence interval; LS Mean: least squares mean; NT-proBNP: N-terminal pro-brain natriuretic peptide.
LS Mean, p-values, estimated difference, and associated 95% CIs were from the mixed model repeated measurement with the change from baseline in log-transformed NT-proBNP as the dependent variable; treatment, week, treatment by week interaction as the fixed effects; and log-transformed baseline NT-proBNP as the covariate. An unstructured variance/covariance structure shared across treatment groups was used to model the within-subject errors.

# Kaplan-Meier Plot of Time to First Clinical Worsening Event


| # Patients at each timepoint | | | | | |
|---|---|---|---|---|---|
| Inhaled Treprostinil | 163 | 151 | 138 | 127 | 93 |
| Placebo | 163 | 152 | 136 | 116 | 87 |

Clinical worsening occurred in 37 patients (22.7%) in the treprostinil group as compared with 54 patients (33.1%) in the placebo group (hazard ratio, 0.61; 95% CI, 0.40 to 0.92; P = 0.04 by the log-rank test).

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CI: confidence interval; HR: hazard ratio
Subjects who discontinued from the study early had their time to clinical worsening censored at their last visit. Subjects who did not experience a clinical worsening event had their time to clinical worsening censored at the study termination date. (1) P-value was calculated with log-rank test stratified by baseline 6MWD category. (2) Hazard ratio, 95% CI, and p-value were calculated with proportional hazards model with treatment and baseline 6MWD (continuous) as explanatory variables.

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# Summary of Clinical Worsening Events

| Occurrence of Clinical Worsening | Inhaled Treprostinil N=163 | Placebo N=163 | P-Value |
|---|---|---|---|
| Any Events | 37 (22.7%) | 54 (33.1%) | 0.04 (1) |
| Hospitalization due to cardiopulmonary indication | 18 (11%) | 24 (14.7%) | |
| Decrease in 6MWD >15% from Baseline | 13 (8%) | 26 (16%) | |
| Death (all causes) | 4 (2.5%) | 4 (2.5%) | |
| Lung transplantation | 2 (1.2%) | 0 | |
| Cox proportional hazards model; HR (95% CI) (2) | 0.61 (0.4, 0.92) | | 0.02 |

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CI: confidence interval; HR: hazard ratio
Subjects who discontinued from the study early had their time to clinical worsening censored at their last visit. Subjects who did not experience a clinical worsening event had their time to clinical worsening censored at the study termination date. (1) P-value was calculated with log-rank test stratified by baseline 6MWD category. (2) Hazard ratio, 95% CI, and p-value were calculated with proportional hazards model with treatment and baseline 6MWD (continuous) as explanatory variables

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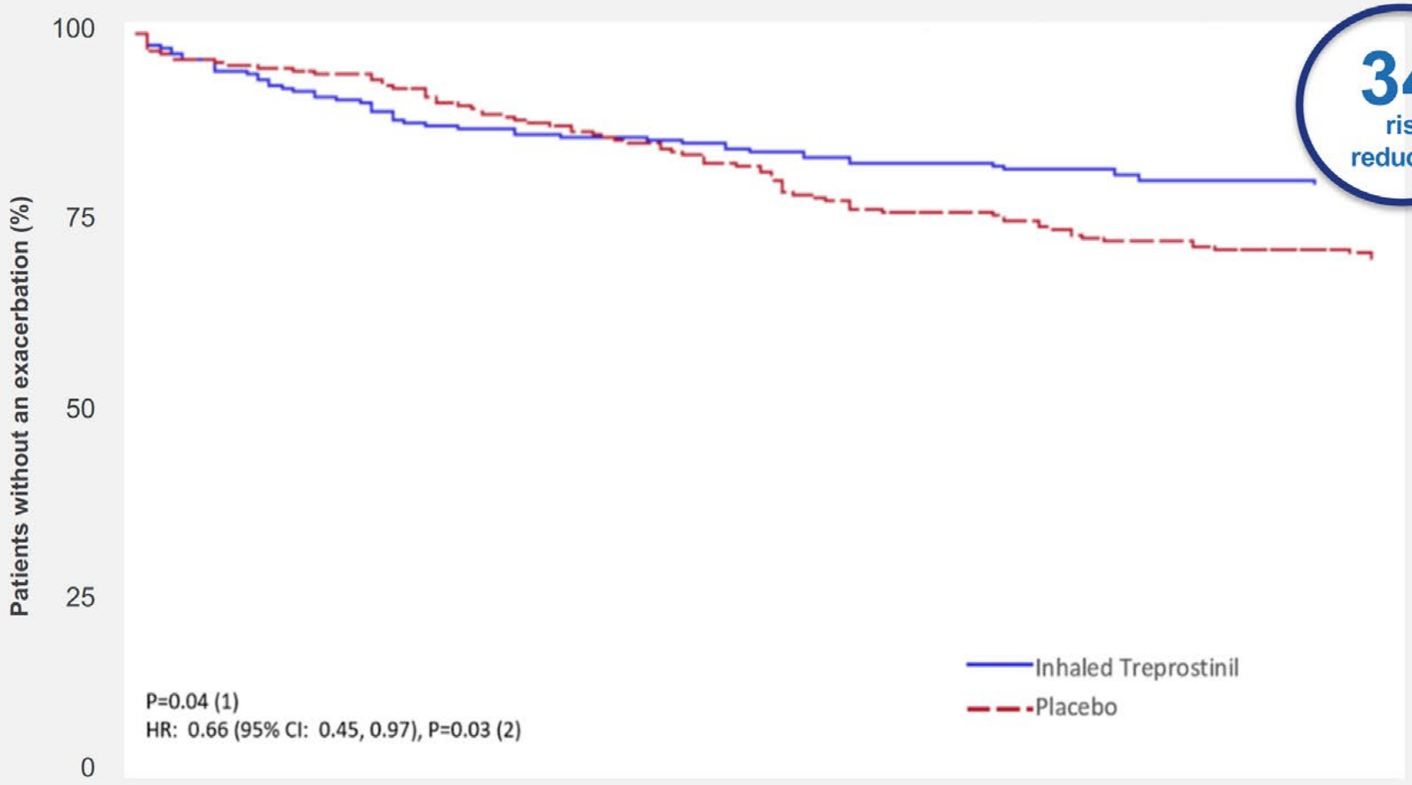
# Kaplan-Meier Plot of Time to Exacerbation of Underlying Lung Disease




| # Patients at each timepoint | | | | | |
|---|---|---|---|---|---|
| Inhaled Treprostinil | 163 | 132 | 119 | 111 | 85 |
| Placebo | 163 | 138 | 117 | 96 | 70 |

Inhaled treprostinil resulted in a 34% reduction in risk of exacerbation of underlying lung disease compared to placebo (P=0.03).

26.4% inhaled treprostinil and 38.7% placebo patients experienced exacerbation of underlying lung disease (P=0.02, Fisher's exact test).

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6MWD: 6-minute walk distance; CI: confidence interval; HR: hazard ratio
Subjects who did not experience an exacerbation had their time to exacerbation censored at the study termination date. (1) P-value was calculated with log-rank test stratified by baseline 6MWD category. (2) Hazard ratio, 95% CI, and P-value were calculated with proportional hazards model with treatment and baseline 6MWD (continuous) as explanatory variables.

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# Safety

Treatment was well tolerated

- Safety profile was consistent with previous studies of inhaled treprostinil
- Most treatment-related AEs were mild to moderate in intensity

10% of inhaled treprostinil and 8% of placebo patients prematurely discontinued treatment due to an AE

Serious AEs occurred in 23.3% of patients receiving inhaled treprostinil and 25.8% of placebo patients

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AE: adverse event.

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# Summary of Adverse Events

| Most Frequently Occurring AEs* | Inhaled Treprostinil N=163 n (%) | Placebo N=163 n (%) |
|---|---|---|
| Cough | 71 (43.6%) | 54 (33.1%) |
| Headache | 45 (27.6%) | 32 (19.6%) |
| **Dyspnea†** | **41 (25.2%)** | **51 (31.3%)** |
| Dizziness | 30 (18.4%) | 23 (14.1%) |
| Nausea | 25 (15.3%) | 26 (16%) |
| Fatigue | 23 (14.1%) | 23 (14.1%) |
| Diarrhea | 22 (13.5%) | 19 (11.7%) |
| Throat irritation | 20 (12.3%) | 6 (3.7%) |
| Oropharyngeal pain | 18 (11%) | 4 (2.5%) |
| **NT-proBNP increased†** | **9 (5.5%)** | **25 (15.3%)** |

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AE: adverse event; NT-proBNP: N-terminal pro-brain natriuretic peptide.
*Most frequently occurring AEs, >10% patients in either group – Safety Population. †Occurred more frequently in patients receiving placebo.

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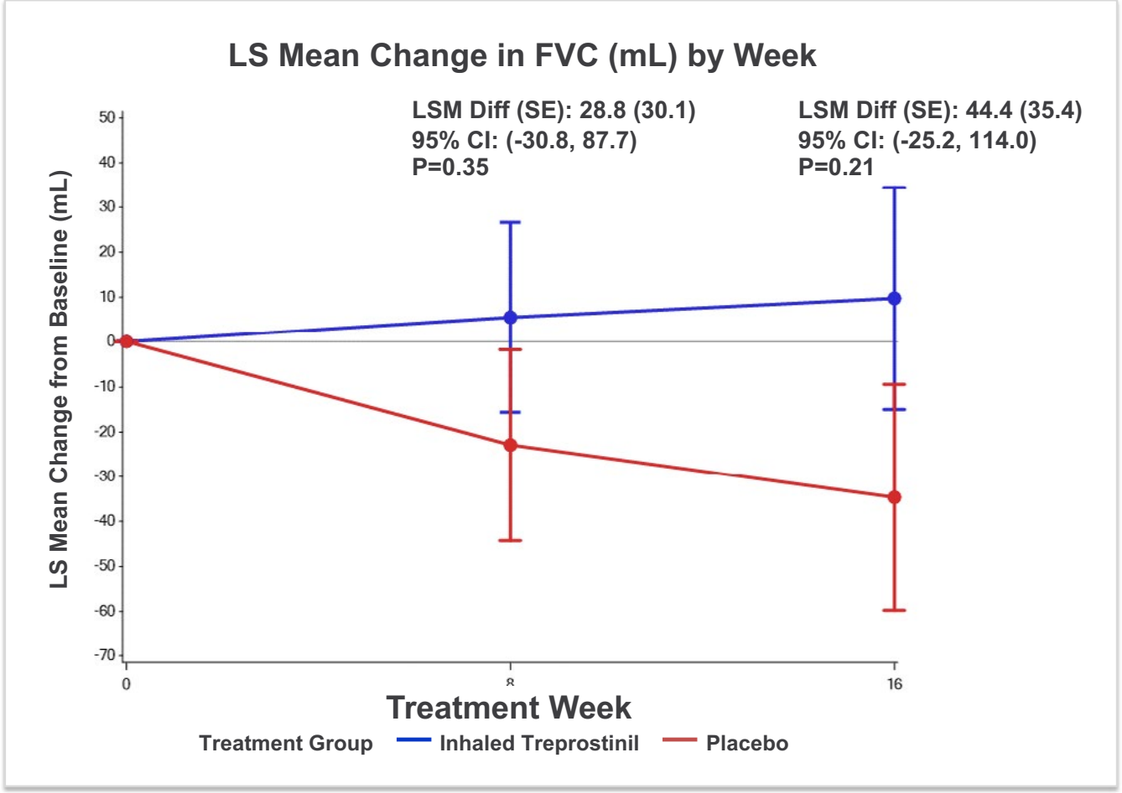
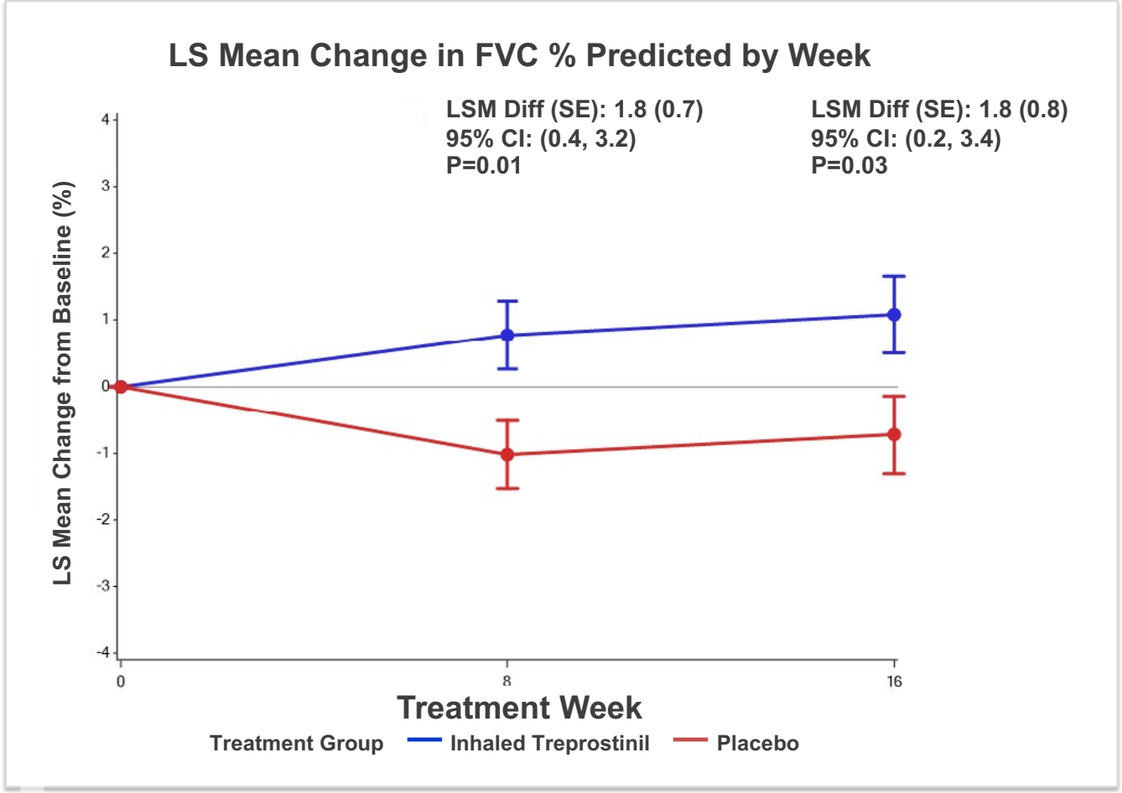
# FVC Results by Study Visit

- Inhaled treprostinil resulted in placebo-corrected improvements in FVC of 28.47 mL and 44.40 mL at Weeks 8 and 16, respectively.
- Percent predicted FVC at Week 8 (1.79%; P=0.01) and Week 16 (1.80%; P=0.03).

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FVC: forced vital capacity; LS Mean: least squares mean; SE: standard error.
LS Mean (SE), P-values, estimated difference (SE), and associated 95% CIs are from the mixed model repeated measurement with the change from Baseline in FVC as the dependent variable; treatment, week, treatment by week interaction as the fixed effects; Baseline FVC as the covariate; and subject as the random effect. An unstructured variance/covariance structure shared across treatment groups was used to model the within-subject errors.

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# Subgroup Analysis of FVC

| PH-ILD Etiology | Variable | Visit | Treatment | LS Mean | Contrast: Inhaled treprostinil - Placebo Estimated Difference (95% CI) | P-value |
|---|---|---|---|---|---|---|
| IIP | FVC (mL) | Week 8 | Inhaled treprostinil (n=58)<br>Placebo (n=71) | 9.27<br>-37.21 | 46.48<br>(-32.55, 125.51) | 0.25 |
| | | Week 16 | Inhaled treprostinil (n=52)<br>Placebo (n=63) | 22.16<br>-86.02 | 108.18<br>(15.25, 201.10) | 0.02 |
| | FVC (% predicted) | Week 8 | Inhaled treprostinil (n=58)<br>Placebo (n=71) | 0.92<br>-1.03 | 1.95<br>(0.12, 3.79) | 0.04 |
| | | Week 16 | Inhaled treprostinil (n=52)<br>Placebo (n=63) | 1.66<br>-1.23 | 2.88<br>(0.72, 5.05) | 0.01 |
| IPF | FVC (mL) | Week 8 | Inhaled treprostinil (n=31)<br>Placebo (n=47) | 41.69<br>-42.83 | 84.522<br>(-20.409, 189.454) | 0.11 |
| | | Week 16 | Inhaled treprostinil (n=28)<br>Placebo (n=42) | 38.24<br>-130.3 | 168.524<br>(40.078, 296.970) | 0.01 |
| | FVC (% predicted) | Week 8 | Inhaled treprostinil (n=31)<br>Placebo (n=47) | 1.60<br>-0.94 | 2.543<br>(0.145, 4.941) | 0.04 |
| | | Week 16 | Inhaled treprostinil (n=28)<br>Placebo (n=42) | 1.62<br>-1.88 | 3.504<br>(0.712, 6.295) | 0.01 |

CI: confidence interval; FVC: forced vital capacity; IIP: idiopathic interstitial pneumonia; ILD: interstitial lung disease; IPF: idiopathic pulmonary fibrosis; LS Mean: least squares mean; PH: pulmonary hypertension.

LS Mean (SE), P-values, estimated difference (SE), and associated 95% CIs are from the mixed model repeated measurement with the change from Baseline in FVC as the dependent variable; treatment, week, treatment by week interaction as the fixed effects; Baseline FVC as the covariate; and subject as the random effect. An unstructured variance/covariance structure shared across treatment groups was used to model the within-subject errors.

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# Additional Safety Endpoints

No clinically relevant treatment-related changes in pulse oximetry or supplemental oxygen use in either group over the study period.

No deleterious effect of inhaled treprostinil on any PFT parameter during the study.

Median improvement in percent predicted FVC at Week 16 in the inhaled treprostinil group (1%) compared to reduction in the placebo group (-1%).

- Inhaled treprostinil resulted in placebo-corrected improvements in FVC of 28.47 mL and 44.40 mL at Weeks 8 and 16, respectively.
  - Percent predicted FVC at Week 8 (1.79%; P=0.01) and Week 16 (1.80%; P=0.03).
- In IPF patients, inhaled treprostinil resulted in placebo-corrected improvements in FVC of 84.52 mL and 168.52 mL at Weeks 8 (n=78) and 16 (n=70), respectively.

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FVC: forced vital capacity; IPF: idiopathic pulmonary fibrosis; PFT: pulmonary function test.

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# Conclusions

- INCREASE is the largest and most comprehensive study of this patient group to date.
- Patients experienced significant improvements in exercise capacity (6MWD) as early as 8 weeks, with effects sustained throughout the 16-week treatment period.
- Patients demonstrated improvements in other clinically meaningful outcomes, including improvements in NT-proBNP and decreased risk of clinical worsening and exacerbation of underlying lung disease.
- Treatment with inhaled treprostinil was well tolerated.
- No evidence of worsened oxygenation or lung function, allaying V/Q mismatch concerns.
  - Evidence of an improvement in FVC.
- Results support an additional treatment avenue and might herald a shift in the clinical management of patients with ILD.

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6MWD: six-minute walk distance; FVC: forced vital capacity; ILD: interstitial lung disease; NT-proBNP: N-terminal pro-brain natriuretic peptide; V/Q: ventilation/perfusion.

INCREASE

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- Peter S. Marshall, MD, Wassim Fares, MD, Yale New Haven Hospital
- Jeremy P. Feldman, MD, Arizona Pulmonary Specialists, Ltd.
- Micah Fisher, MD, The Emory Clinic
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- Alicia Gerke, MD, University of Iowa Hospitals & Clinics; Reda Ebeid Girgis, MD, Spectrum Health Heart & Lung Specialized Care Clinic
- Jeffrey Golden, MD, University of California San Francisco
- Maria Giovanna Trivieri, MD, Radha Gopalan, MD, Mount Sinai Medical Center
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- Antoine Hage, MD, Cedars - Sinai Medical Center
- William Harvey, MD, IU Health Physicians Advanced Heart & Lung Clinic
- Paul Hassoun, MD, Johns Hopkins University, Pulmonary and Critical Care Medicine; Nicholas Hill, MD, Tufts Medical Center
- Lawrence Ho, MD, University of Washington Medical Center
- Ahmed El-Bershawi, MD, Heba Ismail, MD, Pacific Pulmonary Medical Group
- Behrouz Jafari, MD, VA Long Beach Healthcare System; Javier Jimenez, MD, South Miami Heart Specialists; Shilpa Johri, MD, Pulmonary Associates of Richmond, Inc.
- Christopher King, MD, Inova Fairfax Medical Campus
- Tunay Kuru, MD, MedStar Georgetown University Hospital
- Matthew Lammi, MD, Louisiana State University Health Sciences Center – New Orleans
- Jennifer Davel, MD, Navneet Lather, MD, Community Heart and Vascular Facility of Community Hospital East
- Deborah J. Levine, MD, University of Texas Health Science Center
- Dustin R. Fraidenburg, MD, Roberto F. Machado, MD, University of Illinois at Chicago Hospital
- Yolanda Mageto, MD, MPH, Baylor University Medical Center
- Catherine J. Markin, MD, Legacy Medical Group - Pulmonary and Sleep Clinic
- Scott E. Mattson, DO, Lutheran Medical Group
- John W. McConnell, MD, Kentuckiana Pulmonary Associates
- Colleen A. McEvoy, MD, Washington University
- Boris I. Medarov, MD, Albany Medical College
- Lana Melendres-Groves, MD, University of New Mexico
- Jeffrey E. Michaelson, MD, Wellstar Medical Group - Pulmonary Medicine
- Ruth Minkin, MD, New York Methodist Hospital
- Hadi Chohan, MD, Syed I. Mobin, MD, Central Florida Pulmonary Group, PA
- Sydney B. Montesi, MD, Massachusetts General Hospital
- Majid Mughal, MD, McLaren Greater Lansing
- Rachel E. Nisbet, MD, Hamilton Mill Clinical Research
- Amy Olson, MD, National Jewish Health
- Lavannya Pandit, MD, Michael E. DeBakey VA Medical Center
- Joseph Parambil, MD, Cleveland Clinic
- Bela Patel, MD, Memorial Hermann Hospital - Texas Medical Center
- David Poch, MD, USCD Medical Center
- Kenneth W. Presberg, MD, Medical College of Wisconsin/Froedtert Hospital
- Michael A. Pritchett, DO, Pinehurst Medical Clinic
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- Sudarshan Rajagopal, MD, PhD, Duke University Medical Center - Duke South Clinic
- Amresh Raina, MD, Allegheny General Hospital
- Gautam V. Ramani, MD, University of Maryland Medical Center Division of Cardiology
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- Joseph Stevenson, DO, Saint Mary's Regional Medical Center, Saint Mary's Health Network
- John Swisher, PhD, MD, Statcare Pulmonary Consultants
- Roxana Sulica, MD, ICAHN School of Medicine – Mount Sinai Beth Israel
- Arunabh Talwar, MD, FCCP, Northwell Health
- Nitin Y. Bhatt, MD, Rajive Tandon, MD, The Ohio State University Wexner Medical Center
- James Tarver, MD, Florida Hospital
- Thenappan Thenappan, MD, University of Minnesota
- Austin B. Thompson III, MD, Nebraska Medicine
- Fred Umeh, MD, Clinical Research Specialists, LLC
- Rajat Walia, MD, St. Joseph's Hospital and Medical Center
- Aaron B. Waxman, MD, PhD, Brigham and Women's Hospital
- Sheila Weaver, DO, Temple University Hospital, Temple Lung Center
- Joel A. Wirth, MD, Chest Medicine Associates
- Mark Yagan, MD, Saint Luke's Hospital of Kansas City
- Peter Yau, MD, FCCP, Scott & White Memorial Hospital and Clinic
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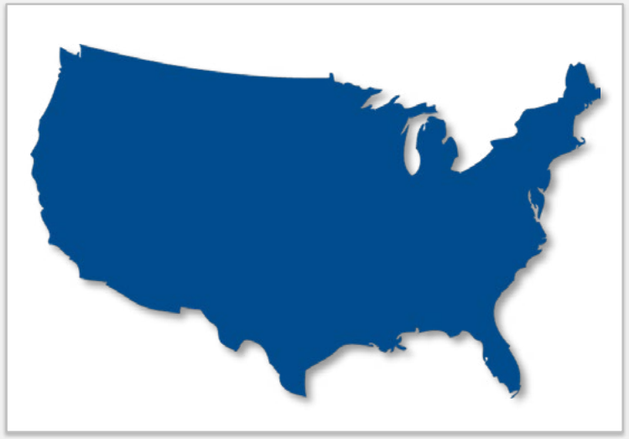

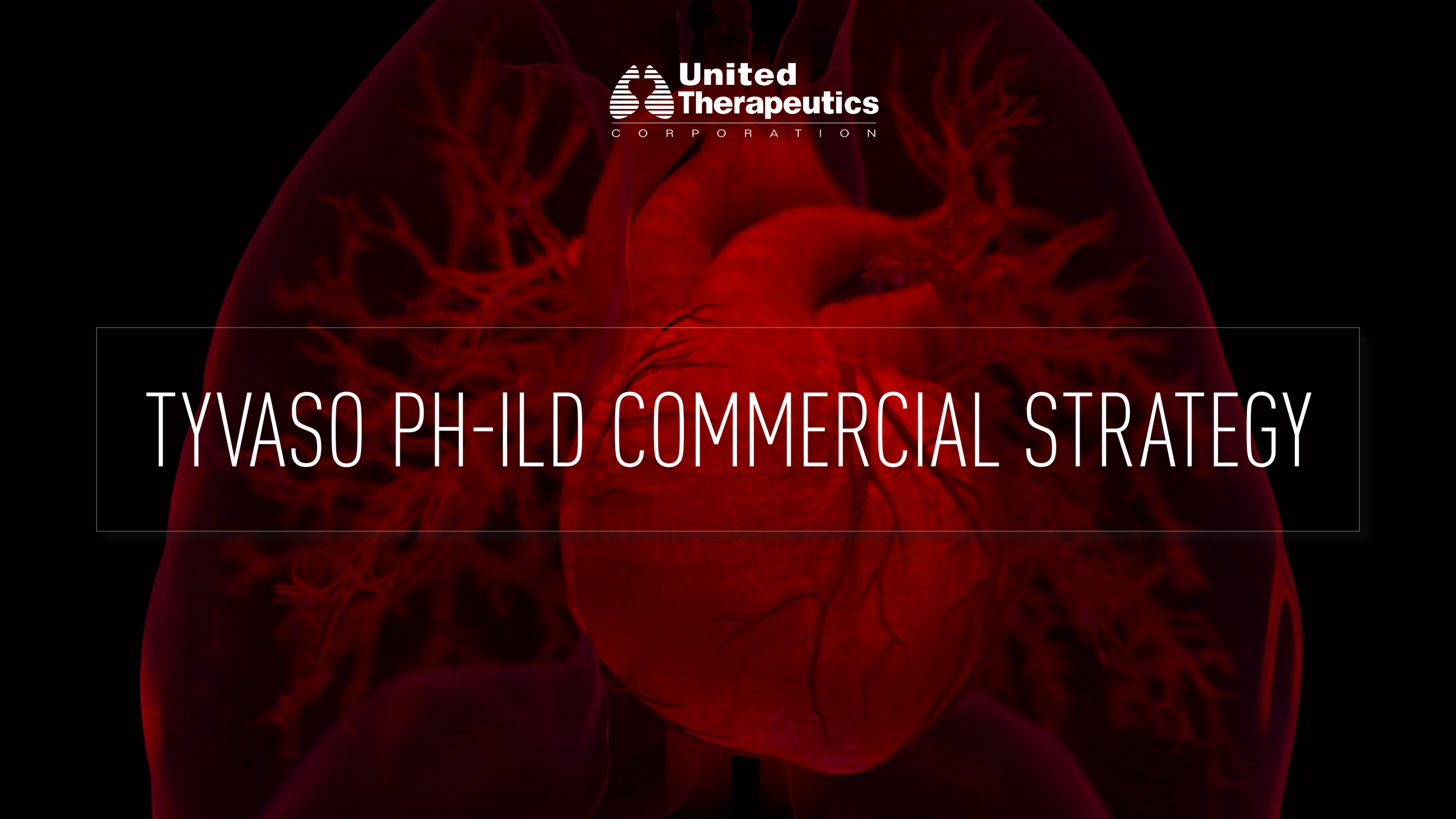

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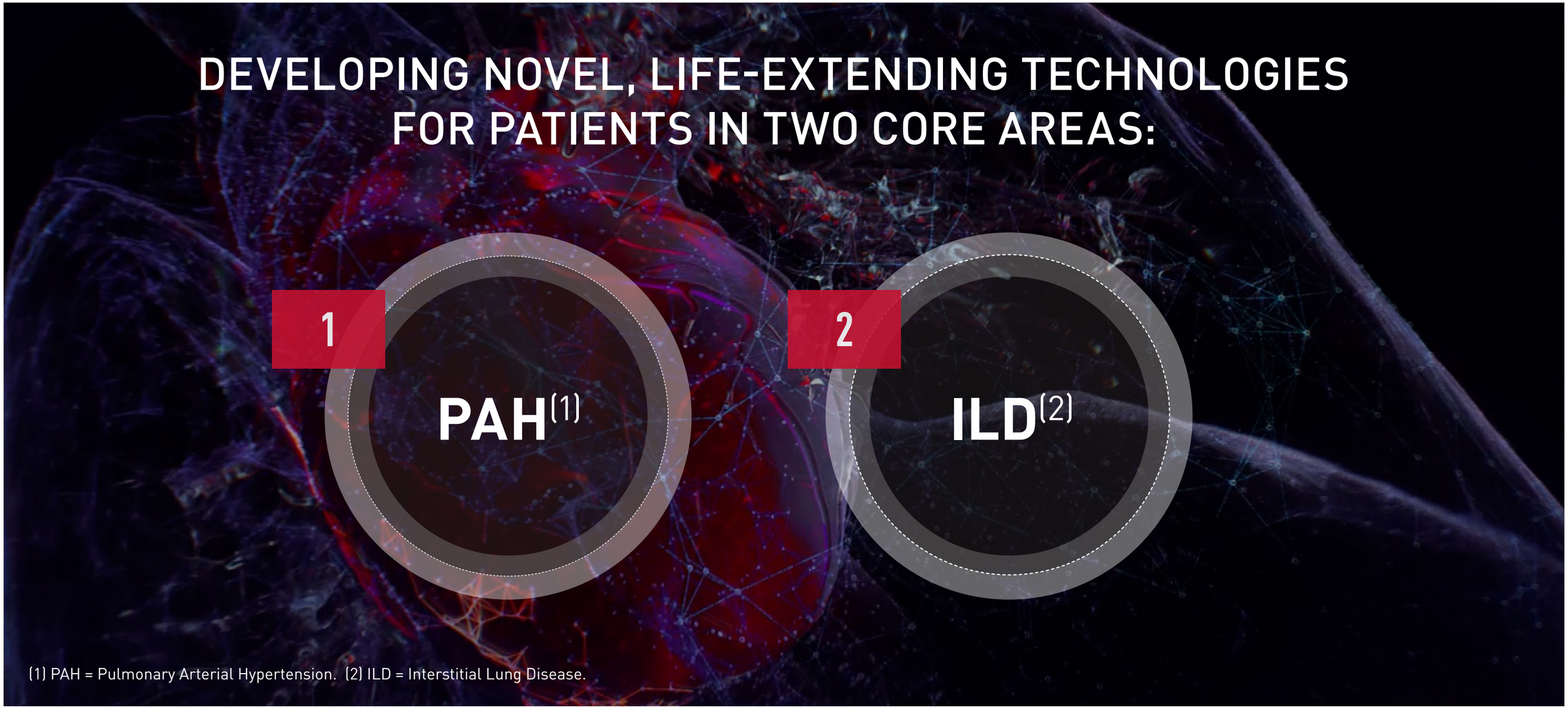
# TYVASO PH-ILD COMMERCIAL STRATEGY

# OUR FOCUS

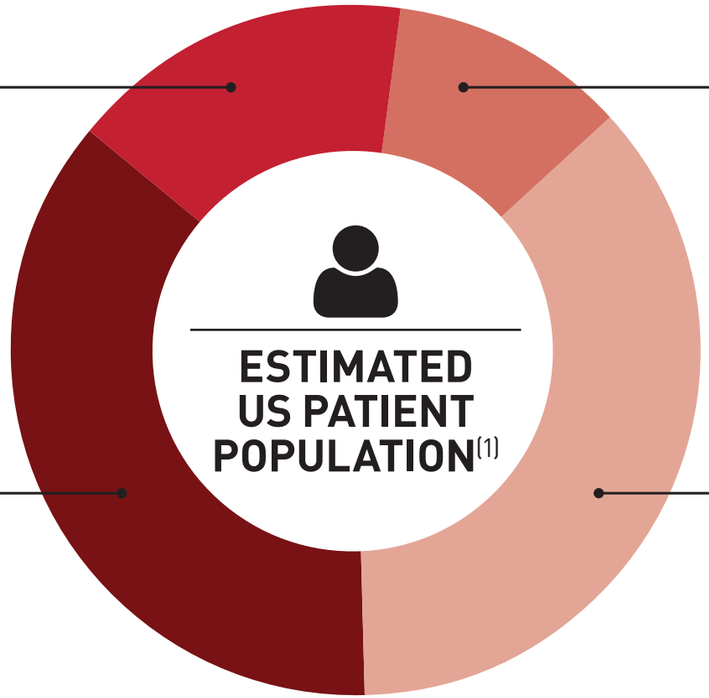



(1) PAH = Pulmonary Arterial Hypertension. (2) ILD = Interstitial Lung Disease.

# TYVASO®[1] PORTFOLIO POSITIONED TO ADVANCE OUR GROWTH

**45K PAH**
Pulmonary Arterial Hypertension

NO DISEASE-MODIFYING RX
**100K IPF**
Idiopathic Pulmonary Fibrosis
**TETON STUDY**




NO APPROVED RX
**30K PH-ILD**
Pulmonary Hypertension associated with Interstitial Lung Disease
**INCREASE STUDY**

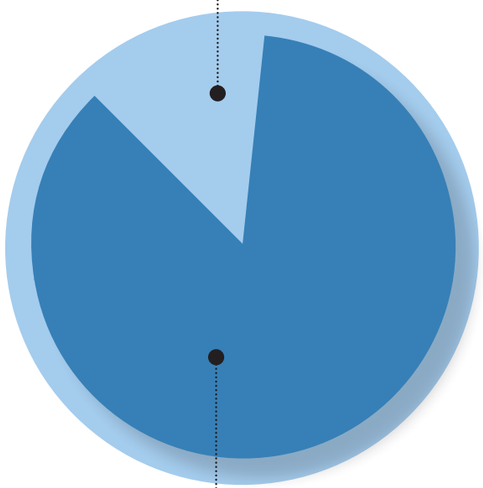
NO APPROVED RX
**100K PH-COPD**
Pulmonary Hypertension associated with Chronic Obstructive Pulmonary Disease
**PERFECT STUDY**

(1) Tyvaso® is not approved for PH WHO Group 3 or IPF patients. (2) Estimated patient populations based on United Therapeutics internal market research.

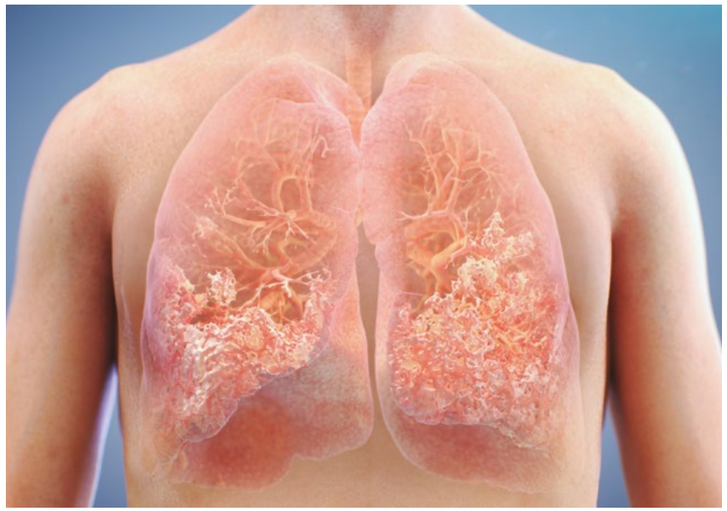
# EPIDEMIOLOGY OF PH-ILD

## PREVALENCE OF PH IN US PATIENTS WITH ILD[1]:

**230K ILD**
~US PATIENT POPULATION[1]



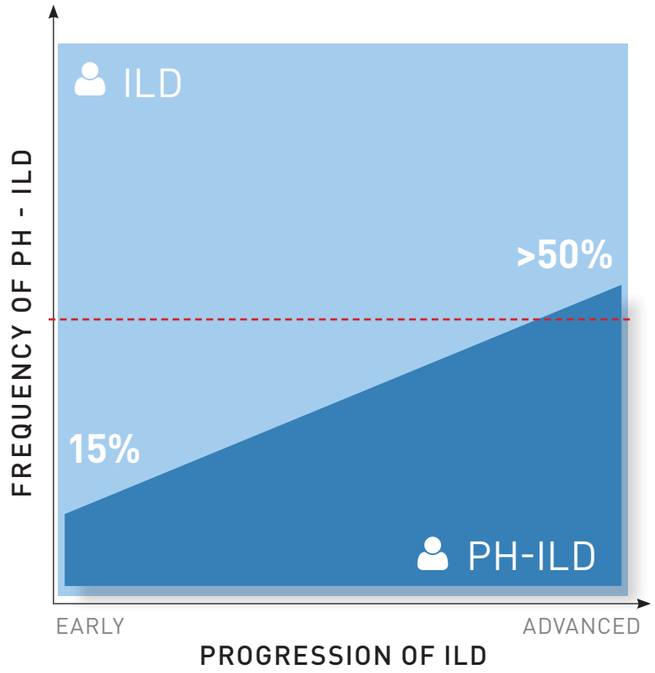
**15%-86%**
COULD DEVELOP
**PH-ILD**[1]



» Precise prevalence of PH in patients with ILD is difficult to establish

- Most of the studies are from case reports and retrospective series

## AS ILD ADVANCES, FREQUENCY OF PH CONTINUES TO RISE, BEYOND 50%[2]

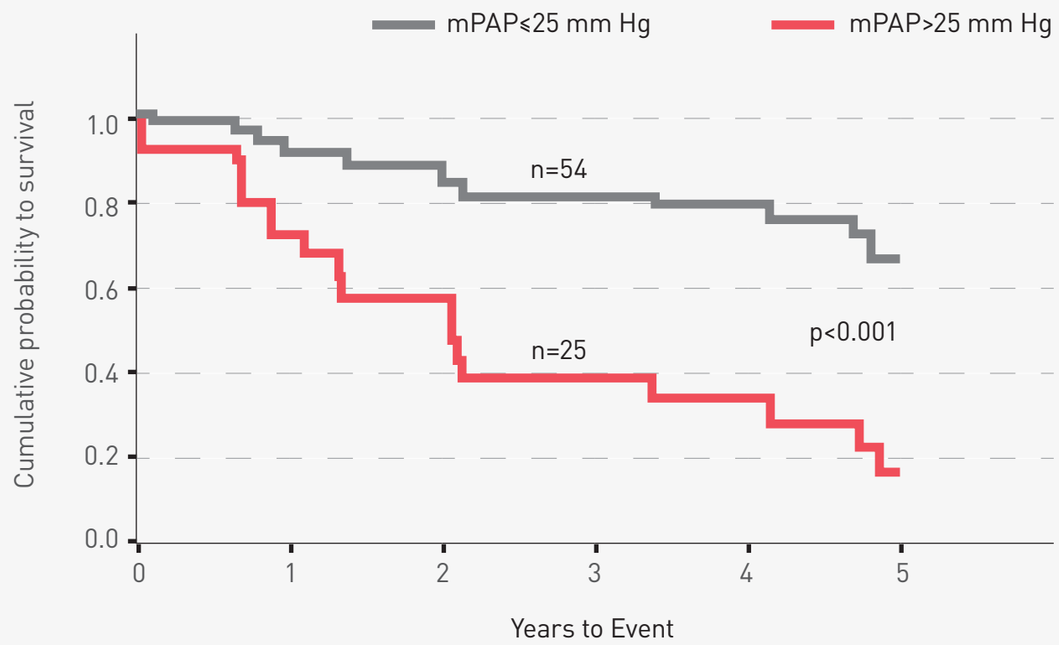



(1) Collum S.D., Amione-Guerra J., Cruz-Solbes A.-S., et al. *Can Respir J*. 2017;2017:1430350. (2) Shorr A.F., Wainwright J.L., Cors C.S., et al. *Eur Respir J*. 2007;30:715–721.
ILD = Interstitial Lung Disease; PH = Pulmonary Hypertension; PH-ILD = Pulmonary Hypertension associated with Interstitial Lung Disease.

# PH SIGNIFICANTLY IMPACTS ILD PATIENT OUTCOMES[1]

## PH changes the trajectory of patient prognosis and may impact ILD treatment choices[2]

### PH REDUCES SURVIVAL IN PATIENTS WITH IPF, A SUBSET OF ILD[3]




### PH REDUCES SURVIVAL IN PATIENTS WITH ILD/IPF

- Based on a study of 79 patients with advanced IPF, a subset of ILD, who were referred for lung transplant evaluation and underwent a right heart catheterization[3]
- PH was defined as mPAP>25 mm Hg[3]
- Average mPAP for the group with PH was 29.5 mm Hg compared with 19.1 mm Hg for the group that did not have PH[3]

### EVEN MILD INCREASES IN mPAP CAN IMPACT PATIENTS WITH ILD/IPF[3]

- About half of patients who have both IPF and PH have slightly elevated mPAP of 25-30 mm Hg[1]

Chart reprinted from Lettieri CJ, et al. Prevalence and outcomes of pulmonary arterial hypertension in advanced idiopathic pulmonary fibrosis. *Chest*. 2006;129(3):746-752. c 2006 with permission from American College of Chest Physicians. **(1)** King CS, Shlobin OA. The trouble with group 3 pulmonary hypertension in interstitial lung disease: dilemmas in diagnosis and the conundrum of treatment. *Chest*. 2020;S0012-3692(20)30872-2. doi:10.1016/j.chest.2020.04.046. **(2)** Nathan SD, Barbera JA, Gaine SP, et al. Pulmonary hypertension in chronic lung disease and hypoxia. *Eur Respir J*. 2019;53(1):1801914. doi:10.1183/13993003.01914-2018. **(3)** Lettieri CJ, Nathan SD, Barnett SD, et al. Prevalence and outcomes of pulmonary arterial hypertension in advanced idiopathic pulmonary fibrosis. *Chest*. 2006;129(3):746-752.
ILD = Interstitial Lung Disease; PH = Pulmonary Hypertension; IPF = Idiopathic Pulmonary Fibrosis. CPFE = Combined pulmonary fibrosis and emphysema; CTD = Connective tissue disease; mPAP=mean pulmonary arterial pressure.

# IDENTIFICATION OF PH-ILD PATIENTS

## SUSPECT

SUSPECT PH-ILD WHEN A PATIENT PRESENTS WITH:

» **Signs and symptoms out of proportion to lung disease**[1,2,3]
- Exacerbations
- Low 6MWD with excessive desaturation and dyspnea
- Low DLCO (<30%-40%)
- PA:A ratio >0.9 (CT)

» **Signs of right ventricular strain or failure**[2,4,5]
- Elevated BNP or NT-proBNP
- Right axis deviation on ECG
- Systolic murmur

## SUPPORT

SUPPORT A SUSPICION OF PH-ILD WITH:

» **Echocardiogram**[1,2,5]
- Elevated sPAP (>45-50 mm Hg)
- Signs of right ventricular dysfunction (eg, RVH)

## CONFIRM

CONFIRM PH-ILD WITH:

» **Right heart catheterization**[2]

» **Hemodynamic definition**[6]
- mPAP ⩾25 mm Hg†
- PAWP ⩽15 mm Hg
- PVR ⩾3 WU

**PH is generally associated with an elevated BNP or NT-proBNP, a lower DLCO, and diminished exercise capacity**[2]

United Therapeutics does not provide medical advice.

†The 2018 World Symposium on Pulmonary Hypertension proposed a cutoff for mPAP of >20 mm Hg.10

PH-ILD = Pulmonary Hypertension associated with Interstitial Lung Disease; 6MWD=6-minute walk distance; BNP=B-type natriuretic peptide; CT=computed tomography; DLCO=diffusing capacity of the lung for carbon monoxide; ECG=electrocardiogram; NT-proBNP=N-terminal pro–B-type natriuretic peptide; PA:A ratio=pulmonary artery to aorta ratio; PAWP=pulmonary arterial wedge pressure; PVR=pulmonary vascular resistance; RVH=right ventricular hypertrophy; sPAP=systolic pulmonary arterial pressure; WU=Wood units.

**(1)** King CS, Shlobin OA. The trouble with group 3 pulmonary hypertension in interstitial lung disease: dilemmas in diagnosis and the conundrum of treatment. *Chest*. 2020;S0012-3692(20)30872-2. doi:10.1016/j.chest.2020.04.046. **(2)** Nathan SD, Barbera JA, Gaine SP, et al. Pulmonary hypertension in chronic lung disease and hypoxia. *Eur Respir J*. 2019;53(1):1801914. doi:10.1183/13993003.01914-2018. **(3)** Judge EP, Fabre A, Adamali HI, et al. Acute exacerbations and pulmonary hypertension in advanced idiopathic pulmonary fibrosis. *Eur Respir J*. 2012;40(1):93-100. **(4)** Ruocco G, Cekorja B, Rottoli P, et al. Role of BNP and echo measurement for pulmonary hypertension recognition in patients with interstitial lung disease: an algorithm application model. *Respir Med*. 2015;109(3):406-415. **(5)** Behr J, Ryu JH. Pulmonary hypertension in interstitial lung disease. *Eur Respir J*. 2008;31(6):1357-1367. **(6)** Simonneau G, Montani D, Celermajer DS, et al. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. *Eur Respir J*. 2019;53(1):1801913. doi:10.1183/13993003.01913-2018.

# PHYSICIANS ARE EAGER FOR TYVASO IN PH-ILD

## Surveys indicate physicians would use Tyvaso for most of their PH-ILD patients[1]

- » INCREASE data will have a **positive impact**[1]
- » HCPs are motivated to **screen more** ILD patients for PH[1]

- » INCREASE data suggests PH-ILD treatment will be augmented with a **new, safe, effective treatment option**[1]
- » HCPs view 6MWD, time to clinical worsening and reduced risk of exacerbations of underlying lung disease endpoints as most impactful[1]

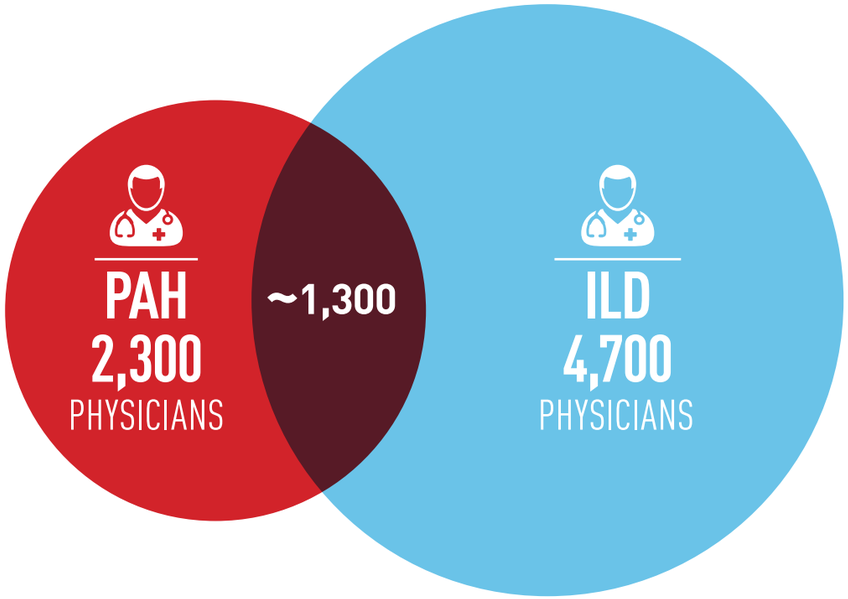
- » Tyvaso has the potential to help **PH-ILD patients improve their condition**[1]

- » Etiologies in INCREASE match providers' patient population[1]
- » Data will **change the way they practice**[1]

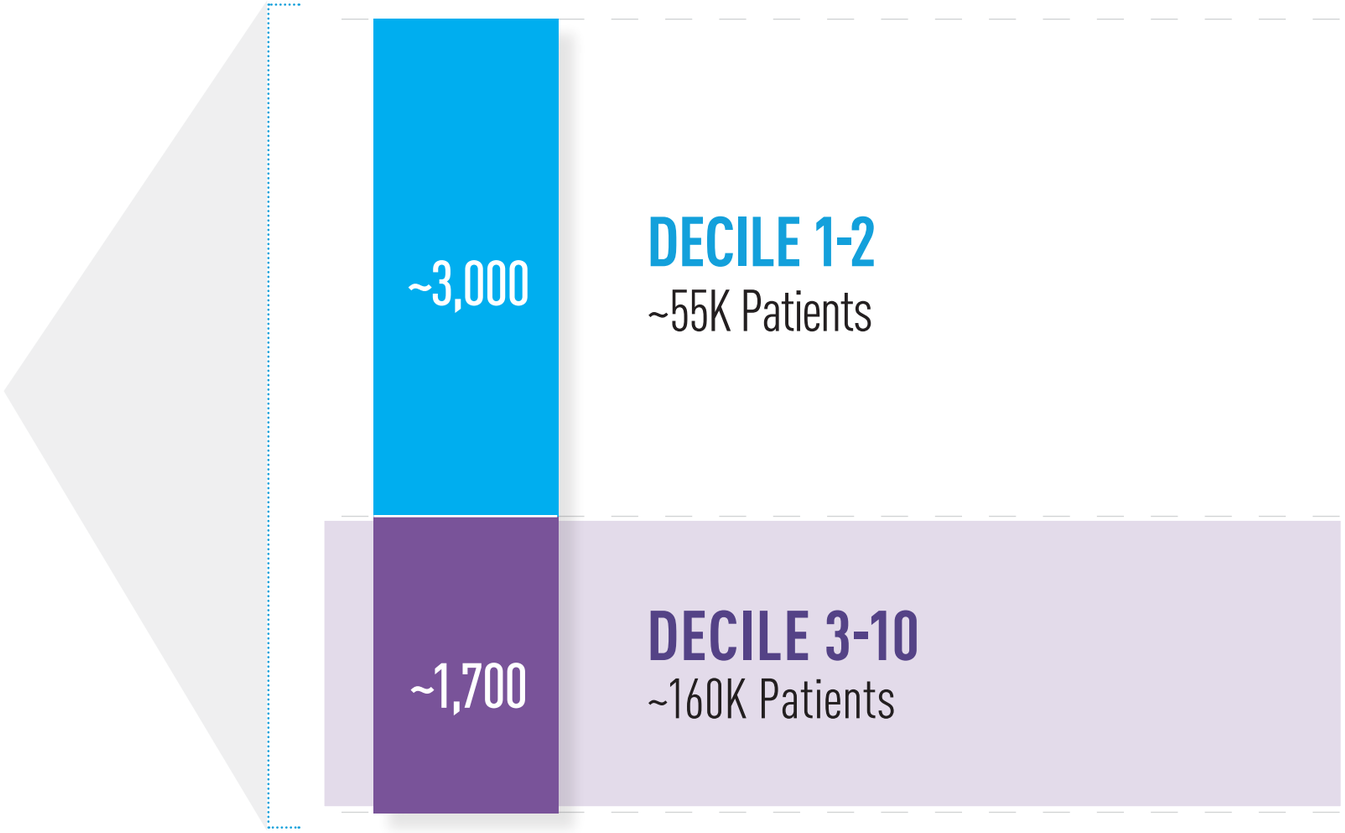
**(1)** Data on file.
ILD = Interstitial Lung Disease; PH = Pulmonary Hypertension; PH-ILD = Pulmonary Hypertension associated with Interstitial Lung Disease; 6MWD=6-minute walk distance.

# MAJORITY OF ILD TREATERS ARE NOT PAH TREATERS

## US PRESCRIBER UNIVERSE




## UNIQUE ILD TREATERS IN US



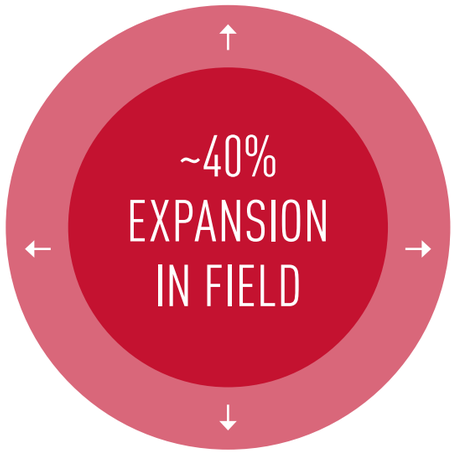

**PAH**
- Higher decile for PAH vs ILD

**PH-ILD**
- Higher decile PH-ILD vs PAH

PAH = Pulmonary Arterial Hypertension; ILD = Interstitial Lung Disease; PH-ILD = Pulmonary Hypertension associated with Interstitial Lung Disease.

# EXPANDING OUR COMMERCIAL/MEDICAL ORGANIZATION FOR PH-ILD

**~40% EXPANSION**
IN FIELD-BASED STAFF INCLUDING SALES, MEDICAL SCIENCE LIAISONS, AND NURSE SPECIALISTS




**RESTRUCTURED SALES ORGANIZATION** WITH THREE TEAMS:

**A**
Orenitram® and Tyvaso in PAH

**B**
Remodulin®

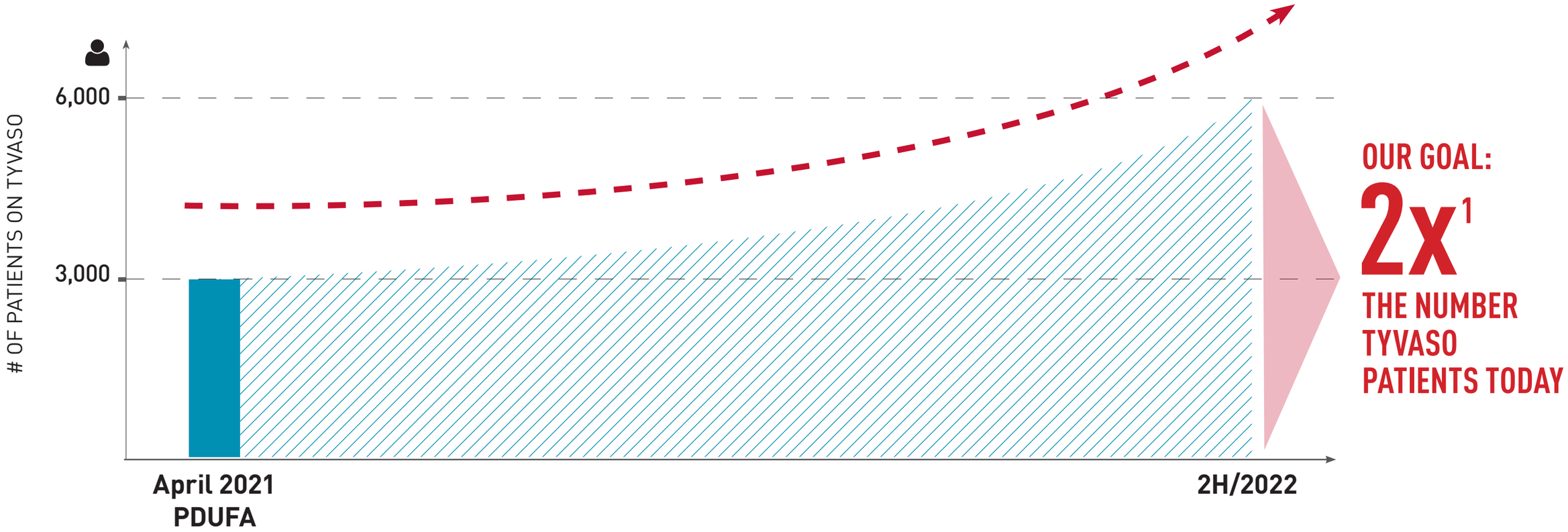
**C**
Tyvaso in PH-ILD

**HIRING IS COMPLETE**

PH-ILD = Pulmonary Hypertension associated with Interstitial Lung Disease; PAH = Pulmonary Arterial Hypertension.

# PLANNING FOR RAPID TYVASO PH-ILD UPTAKE

If approved for PH-ILD, we expect to double the number of Tyvaso® patients within ~18 months of launch




(1) 2x goal assumes an April 2021 sNDA approval and no COVID-19 related impacts to patient access to HCPs and starting therapy. PH-ILD = Pulmonary Hypertension associated with Interstitial Lung Disease.

# KEY SUMMARY POINTS

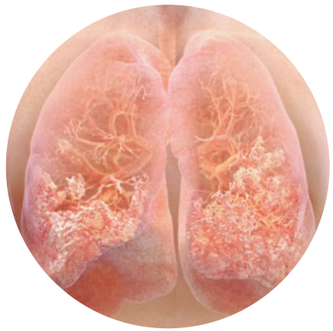
>30K

**ADDRESSABLE MARKET OF >30K PATIENTS WITH NO APPROVED THERAPIES**

**PHYSICIANS INDICATE INCREASE DATA IMPACTFUL AND PLAN TO USE TYVASO FOR PH-ILD PATIENTS**

~ 40% EXPANSION IN FIELD

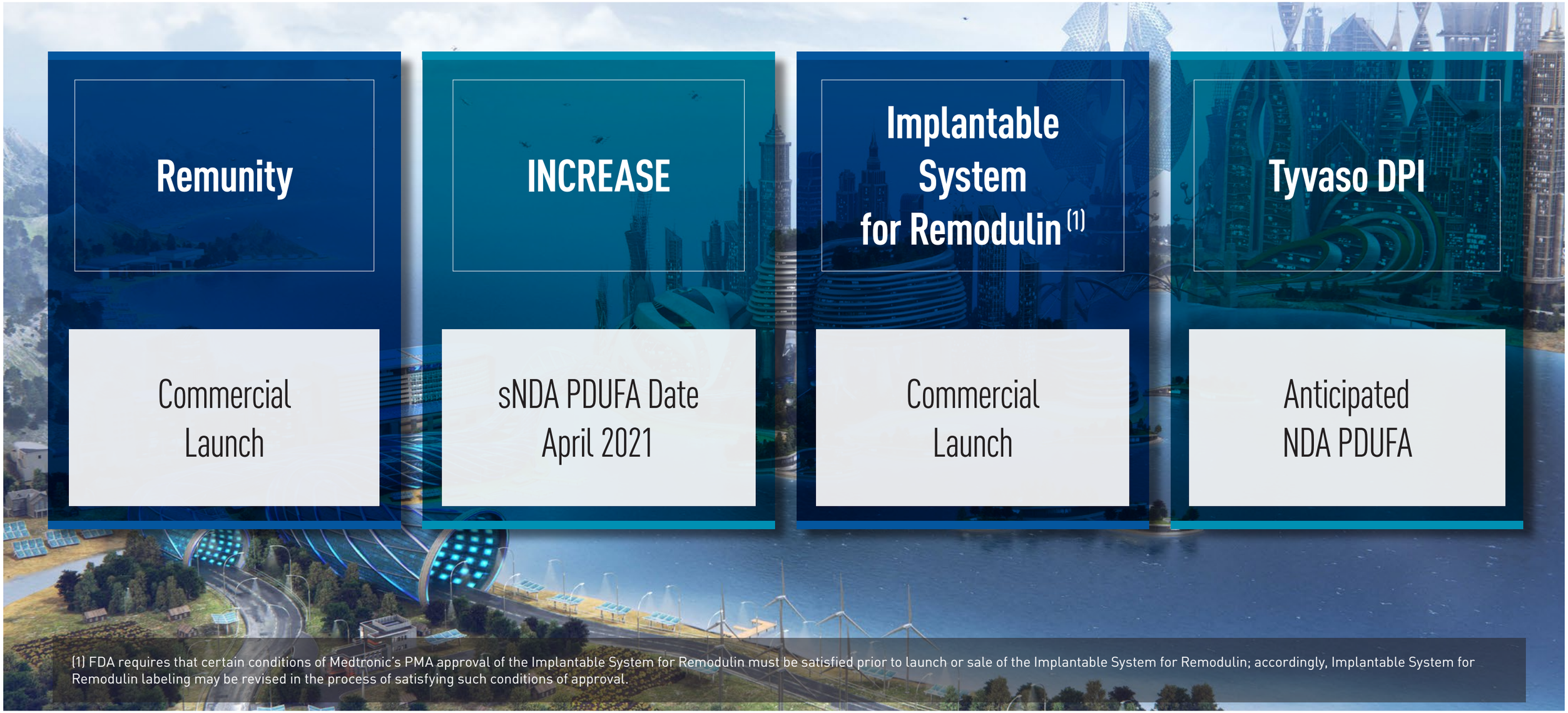
**UT STAFF EXPANSION TO SUPPORT LAUNCH IS COMPLETE**



**EFFORTS UNDERWAY TO INCREASE AWARENESS ON PH IMPACT AND NEED TO SCREEN EARLY**

PH = Pulmonary Hypertension; PH-ILD = Pulmonary Hypertension associated with Interstitial Lung Disease.

# KEY 2021 CATALYSTS



| Remunity | INCREASE | Implantable System for Remodulin [1] | Tyvaso DPI |
|---|---|---|---|
| Commercial Launch | sNDA PDUFA Date April 2021 | Commercial Launch | Anticipated NDA PDUFA |

(1) FDA requires that certain conditions of Medtronic's PMA approval of the Implantable System for Remodulin must be satisfied prior to launch or sale of the Implantable System for Remodulin; accordingly, Implantable System for Remodulin labeling may be revised in the process of satisfying such conditions of approval.

# Q & A

## MICHAEL BENKOWITZ

President and Chief Operating Officer
United Therapeutics Corporation

## JAMES EDGEMOND

Chief Financial Officer and Treasurer
United Therapeutics Corporation

## DEWEY STEADMAN

Head of Investor Relations
United Therapeutics Corporation

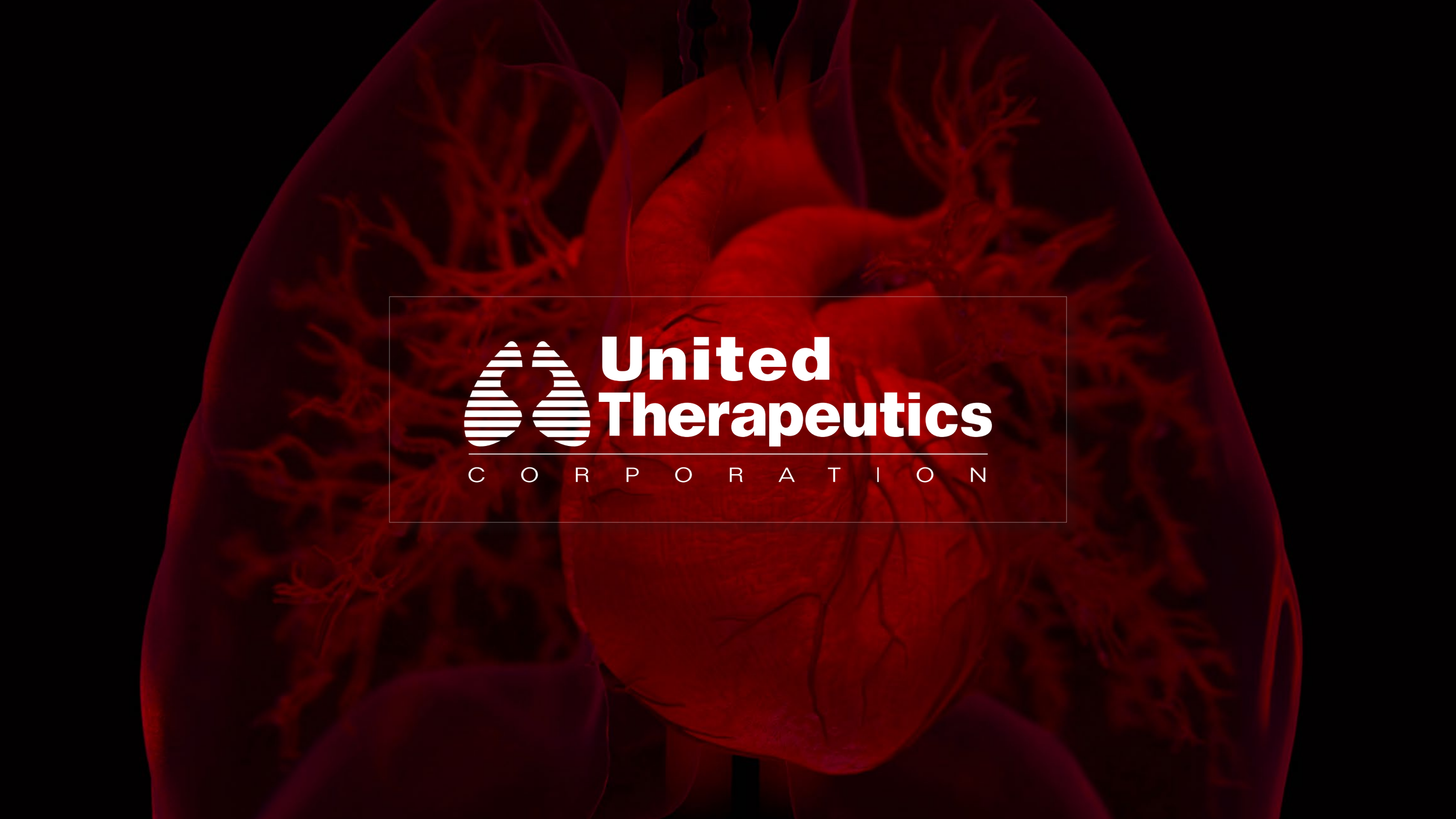
## STEVEN D. NATHAN, MD

INCREASE Study Investigator

Director of the Advanced Lung Disease Program and Director of the Lung Transplant Program at Inova Fairfax Hospital in Falls Church, VA

## LEIGH PETERSON, PhD

Vice President, Product Development
United Therapeutics Corporation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