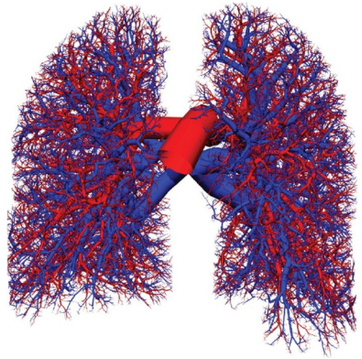

Pulmonary Vascular Disease Program

Brigham and Women's Hospital

Harvard Medical School

Assessment and Treatment of Pulmonary Hypertension

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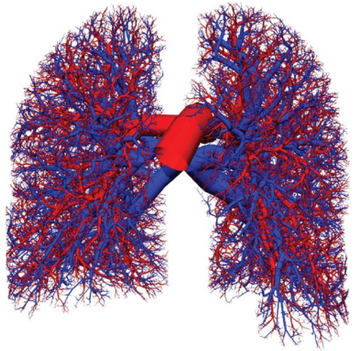

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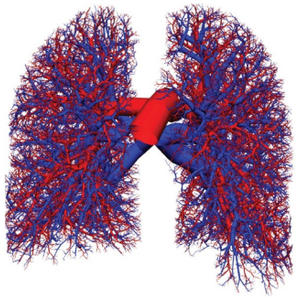
- Disclosures
- Clinical Trial Steering Committees
  - Delivery Trial – United Therapeutics and Medtronic - PI
  - INCREASE Trial – United Therapeutics - PI
  - PERFECT Trial – United Therapeutics - PI
  - Sotatercept Trial – Acceleron
  - ASPIRE Trial – Aria CV - PI



Pulmonary Vascular Disease Program

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- Learning Objectives
  - Updates on Pulmonary Hypertension definition and approach to diagnosis
  - Therapeutic options
  - Selection of appropriate combinations of PAH therapy based on empirical data
  - Expanding the treatment horizon

Diagnosis of PAH

- Signs and symptoms may be subtle and nonspecific
- Clinical suspicion is based on symptoms, risk factors, and medical and family history
- The most common symptoms include exertional dyspnea, fatigue, weakness, light-headedness/syncope, and chest pain
- At more advanced disease stages, there may be signs and symptoms of cardiovascular abnormalities
- Diagnostic and screening tools to confirm PH are shown here

Key Diagnostic Tools

- Electrocardiography (ECG)
- Pulmonary function tests (PFT)
- Cardiopulmonary exercise testing (CPET)
- Ventilation/perfusion (V/Q) lung scanning
- Chest computed tomography (CT)
- Echocardiography
- Right heart catheterization (RHC)
- N-terminal pro B-type natriuretic peptide (NTProBNP)/BNP for risk assessment

Frost A, et al. *Eur Respir J.* 2019 Jan 24;53(1). pii: 1801904.

Hemodynamic Definitions of PH

	5th WSPH[1]	6th WSPH[2]
PH	mPAP ≥25 mm Hg at rest during RHC	mPAP >20 mm Hg
Pre-capillary PH	mPAP ≥25 mm Hg PAWP ≤15 mm Hg PVR >3 WU	mPAP >20 mm Hg PAWP ≤15 mm Hg PVR ≥3 WU

mPAP: mean pulmonary arterial pressure; PAWP: pulmonary arterial wedge pressure; PVR: pulmonary vascular resistance; RHC: right heart catheterization; WU: Wood Units. **Pre-capillary PH is included in clinical groups 1, 3, 4 and 5.[2]**

1. Hoeper MM, et al. J *Am Coll Cardiol.* 2013;62:D42-D50.
2. Simonneau G, et al. *Eur Respir J*. 2019 Jan 24;53(1). pii: 1801913.

Hemodynamic Definitions of PH

Definitions	Characteristics	Clinical Groups[a]
Isolated post-capillary PH (IpcPH)	mPAP >20 mm Hg PAWP >15 mm Hg PVR <3 WU	2 and 5
Combined pre- and post-capillary PH (CpcPH)	mPAP >20 mm Hg PAWP >15 mm Hg PVR ⩾3 WU	2 and 5

[a]Group 1: PAH; group 2: PH due to left heart disease; group 3: PH due to lung diseases and/or hypoxia; group 4: PH due to pulmonary artery obstructions; group 5: PH with unclear and/or multifactorial mechanisms.

Simonneau G, et al. *Eur Respir J*. 2019 Jan 24;53(1)

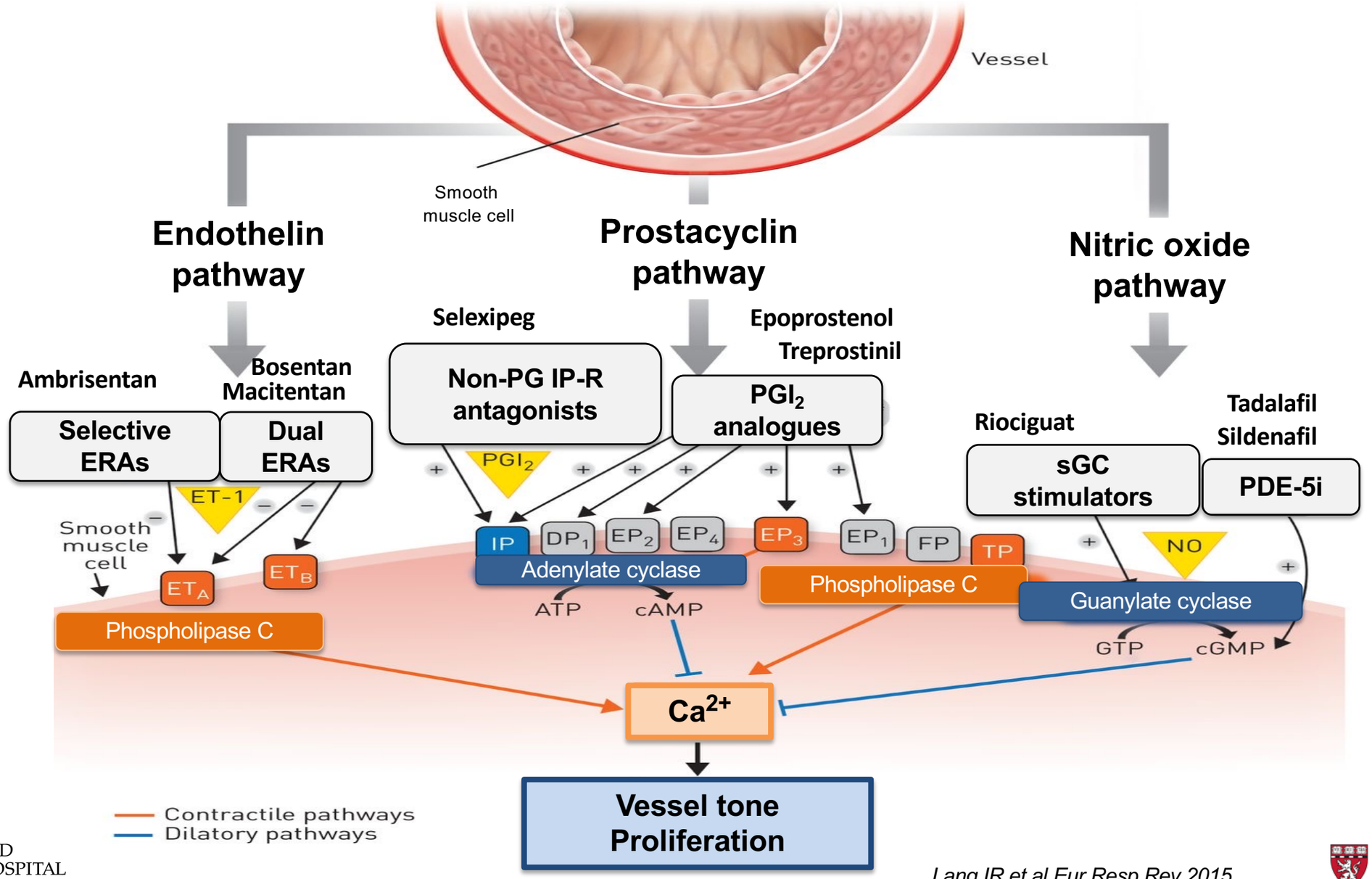
Treatment Algorithm

General Measures	Supportive Therapy
• Avoid pregnancy • Influenza and pneumococcal immunization • Psychological counseling • Supervised exercise training • Supplemented oxygen • Regional anesthesia preferred over general anesthesia	• Diuretics • Long-term oxygen therapy • Anticoagulant therapy • Iron deficiency correction • Use of ACEi, AT1-antagonists, β-blockers, ivabradine only if specifically indicated • Treatment of arrhythmias

Note: **Oral anticoagulant therapy is not recommended in associated forms of PAH, while in IPAH, HPAH and DT-PAH the data on efficacy is more conflicting**. The decision about anticoagulation has to be made on a case-by-case basis after an individual risk–benefit analysis.

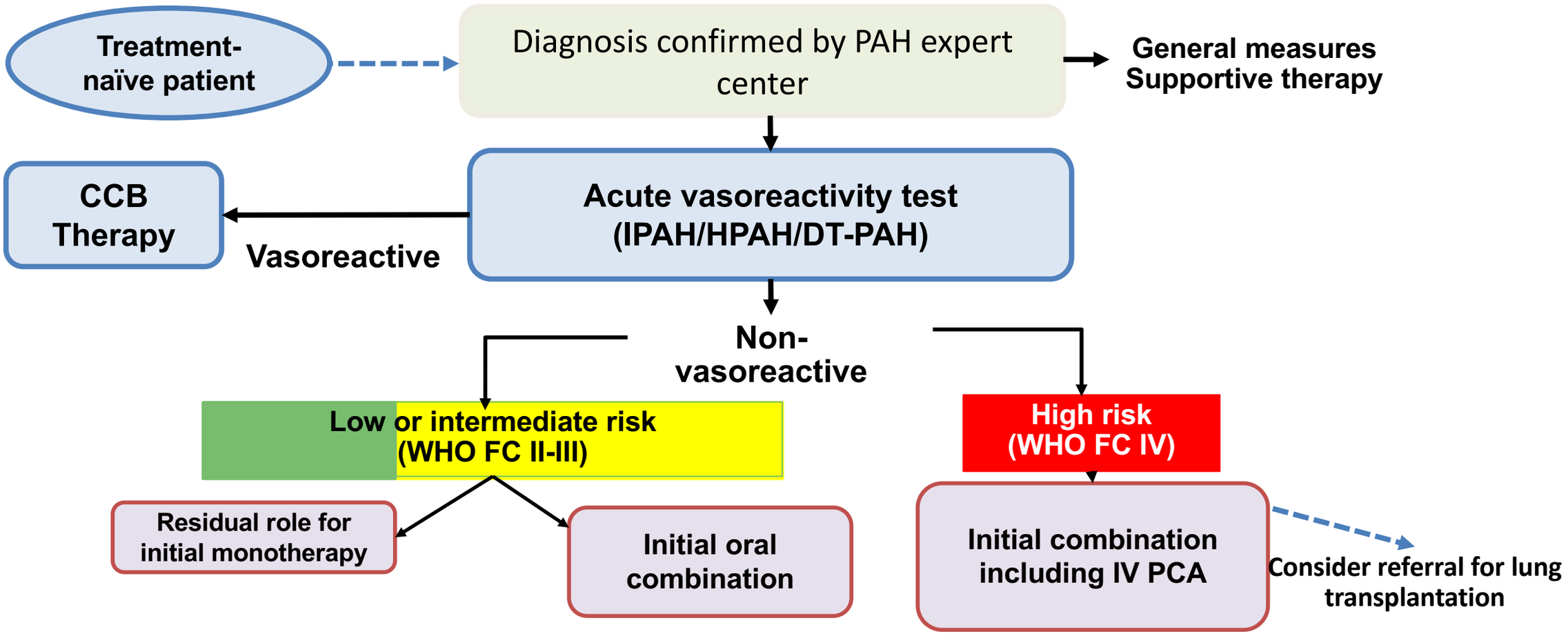
Galié N, et al. *Eur Respir J*. 2016;37:67–119.

Current Therapeutic Targets in PAH



Lang IR et al Eur Resp Rev 2015

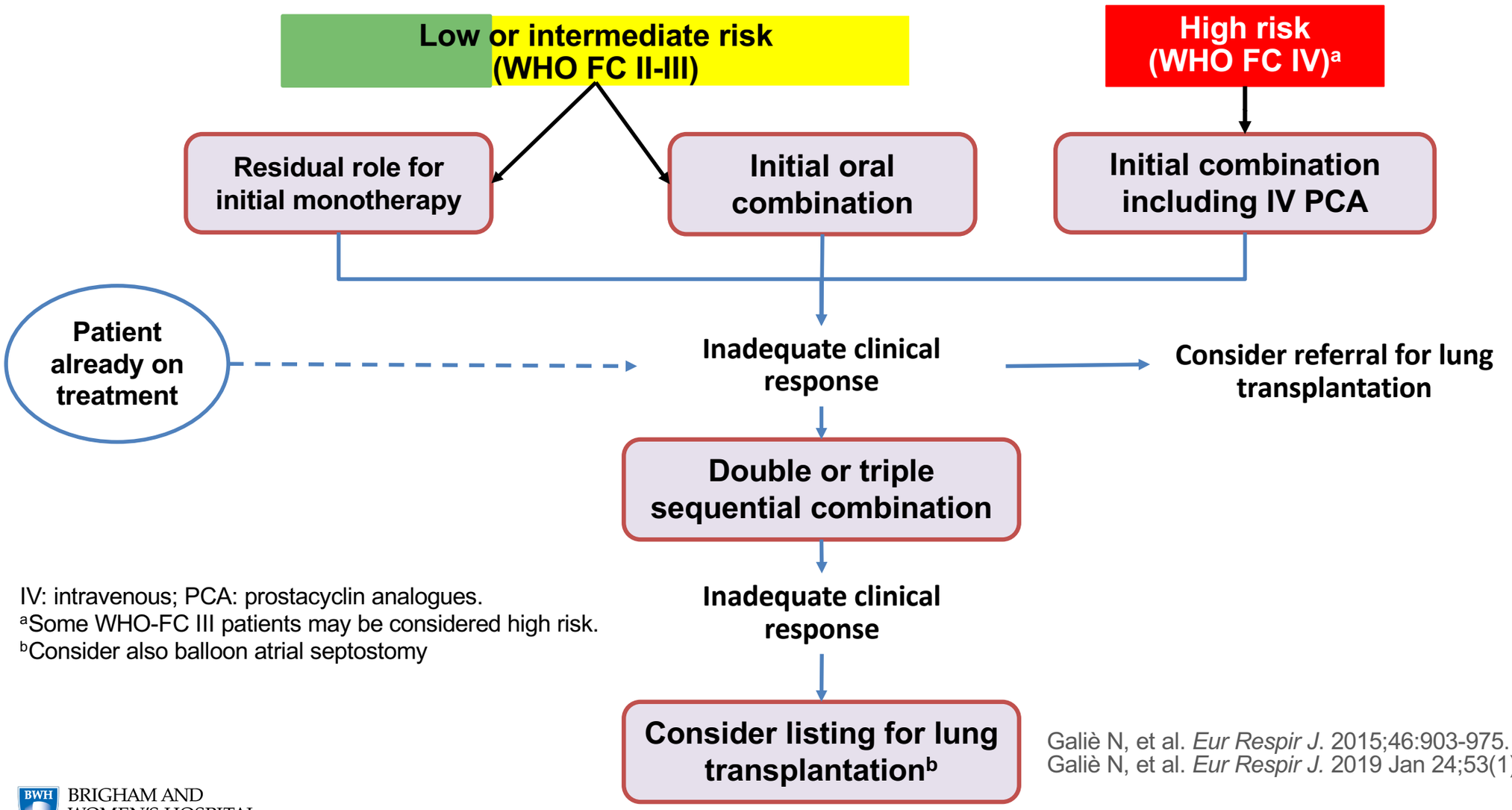
Treatment Algorithm for Initial PAH-Specific Therapy



IV: intravenous; PCA: prostacyclin analogues.

Galiè N, et al. *Eur Respir J*. 2015;46:903-975.
Galiè N, et al. *Eur Respir J*. 2019 Jan 24;53(1). pii: 1801889.

Treatment Algorithm for Initial PAH-Specific Therapy



IV: intravenous; PCA: prostacyclin analogues.
[a]Some WHO-FC III patients may be considered high risk.
[b]Consider also balloon atrial septostomy

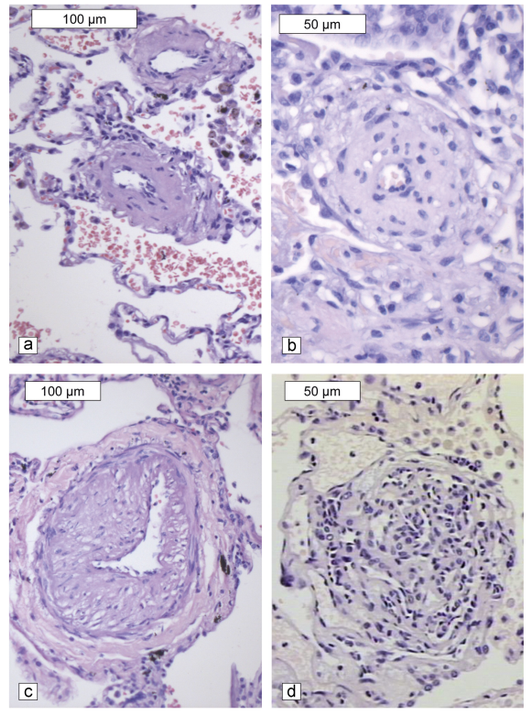
Galiè N, et al. *Eur Respir J.* 2015;46:903-975.
Galiè N, et al. *Eur Respir J.* 2019 Jan 24;53(1). pii: 1801889.

Expected Adverse Effects of PAH-Specific Therapies

- Most PAH medications have class-related adverse effects, often due to vasodilatory properties of the medications
  - ERAs
    - Edema
  - PDE-5 inhibitors
    - Flushing, headache
  - Prostacyclins
    - Headache, flushing, jaw pain, nausea
  - Riociguat (sGC inhibitor)
    - Flushing, headache
  - Selexipag (IP receptor agonist)
    - Headache, flushing, nausea
- In addition, PAH medications are often up-titrated on the basis of tolerability

Group 3 PH - Statement of the Problem

- WHO Group-3PH is frequently encountered and adversely affects patients' quality of life and survival.
- Pulmonary vascular remodeling is a component of advanced lung disease and probably reflects the inflammatory nature of the disease

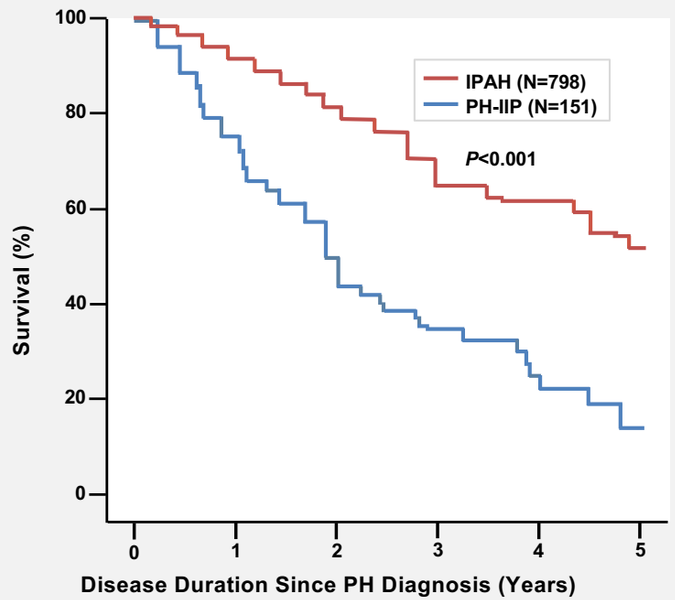


The Journal of Heart and Lung Transplantation 2013; 32:347-354

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.

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, 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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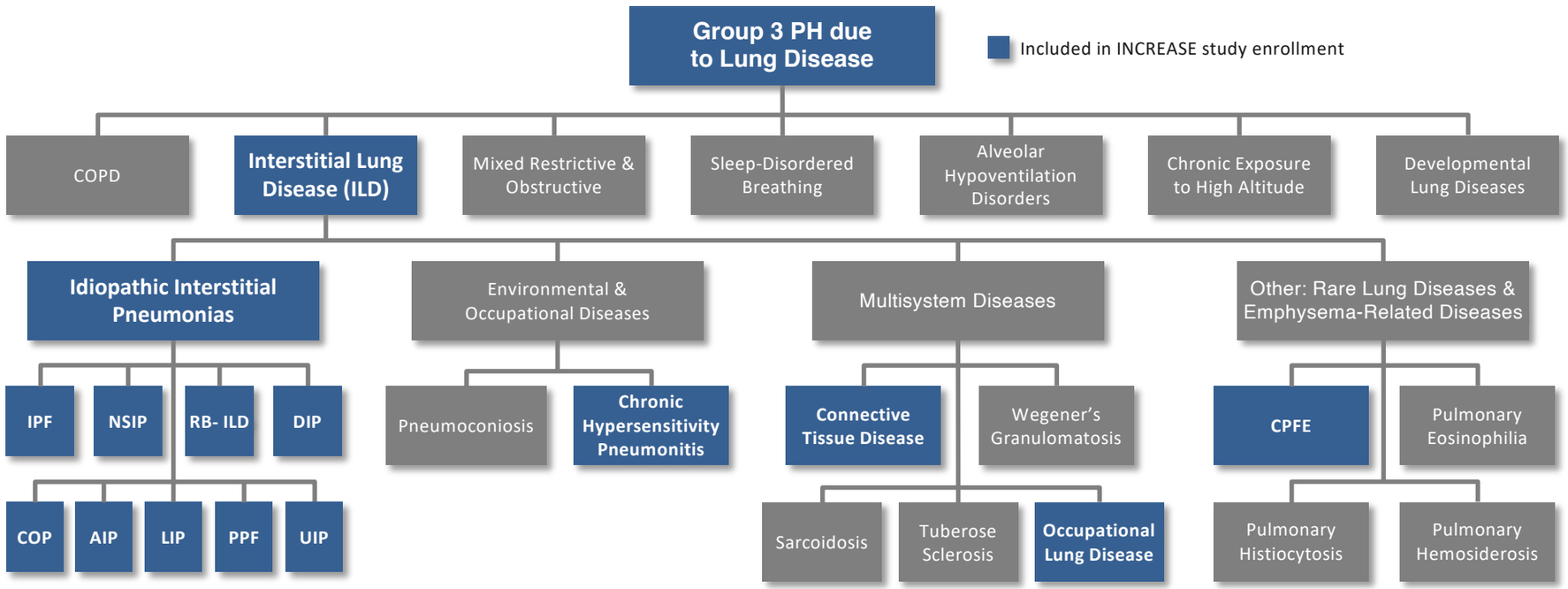
INCREASE Eligible Study Population



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

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

SGRQ: St. George's Respiratory Questionnaire.

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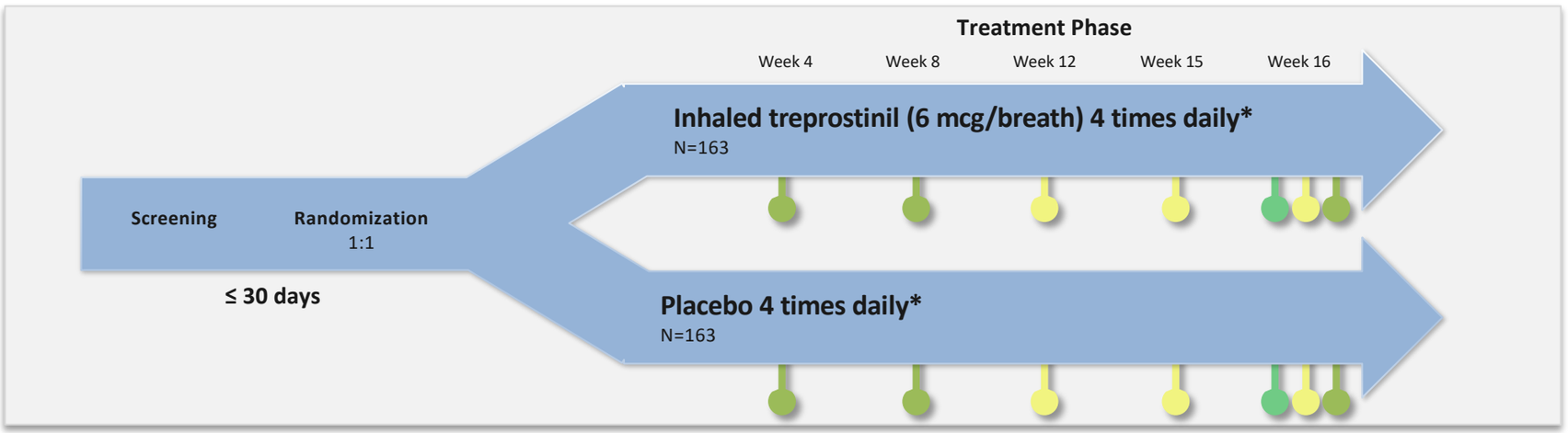
INCREASE – Study Procedures

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

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

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Baseline Characteristics

- A total of 326 patients were enrolled in the study.
- The most common PH-ILD etiologies included:
  - Idiopathic interstitial pneumonia (45%)
  - Idiopathic pulmonary fibrosis (28%)
- 14% of patients were on single background therapy with pirfenidone and 9% on nintedanib
- The median dose of inhaled treprostinil achieved at Week 8 and Week 16 were 10 and 12 breaths per session, respectively.

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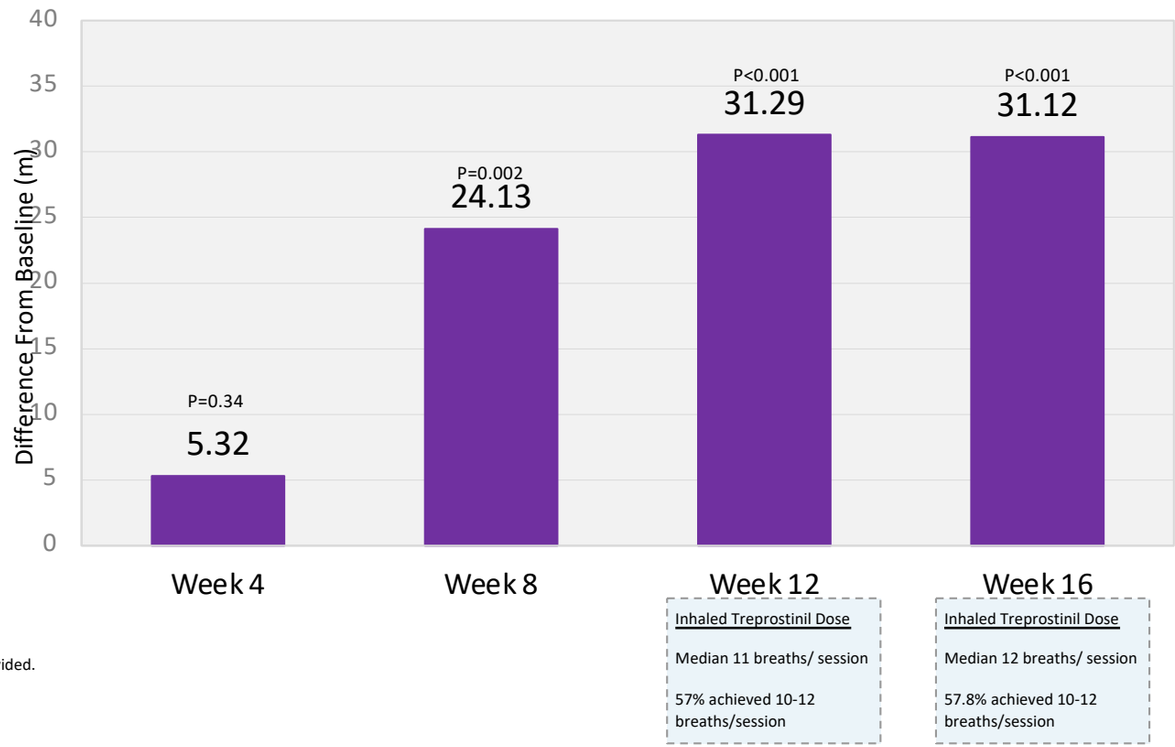
6MWD Results Through Week 16

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).



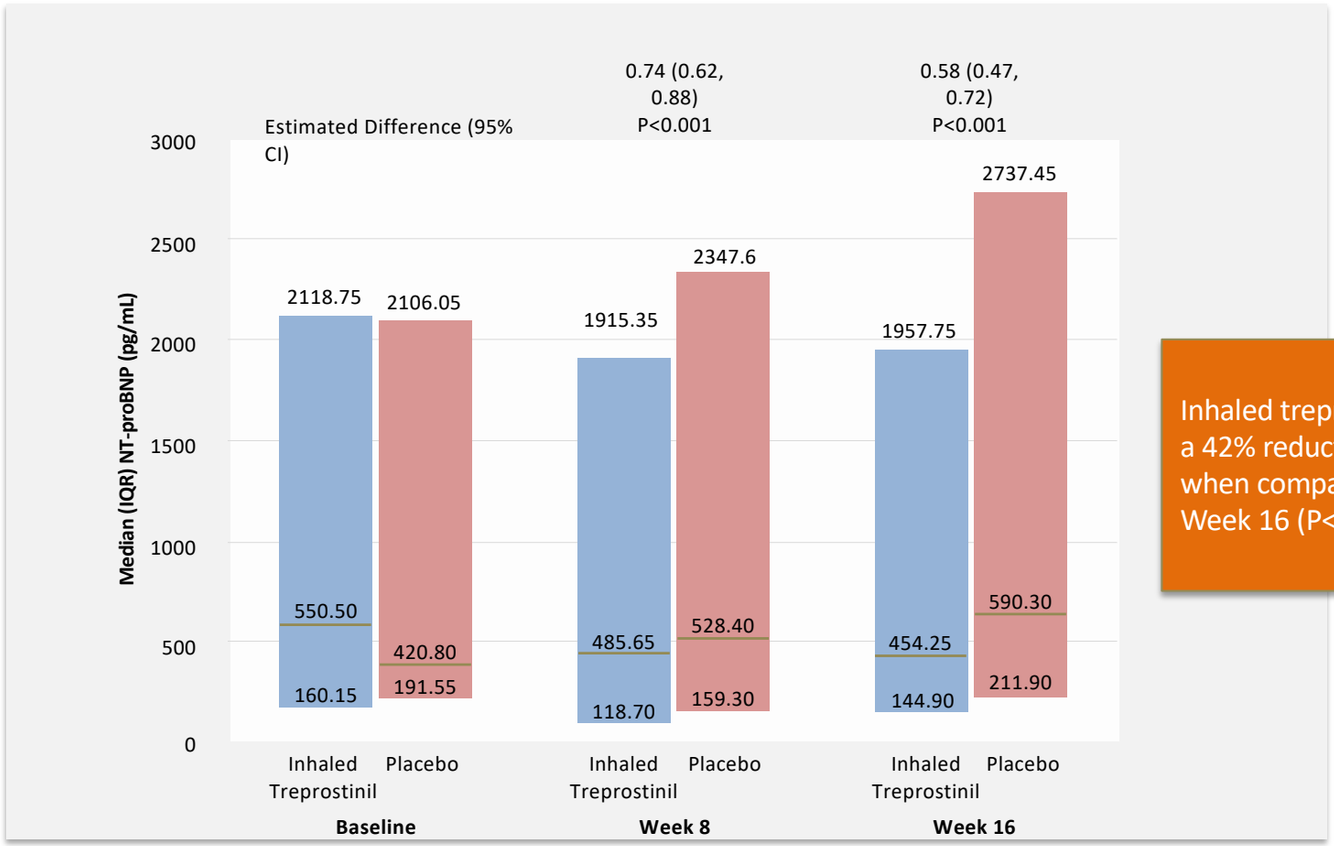
Mixed Model Repeated Measurement treatment effect is provided.
6MWD, 6-Minute Walk Distance; m, meter.

Subgroup Analyses of Peak 6MWD at Week 16

Subgroup	Inhaled Treprostinil # Patients	Placebo # Patients	Hodges-Lehmann Estimate (95% CI)
All Patients	163	163	21.0 (7.0, 37.0)
Age Group			
<65 years	64	48	11.0 (-11.0,46.0)
65 to 80 years	83	100	27.0 (7.0, 46.0)
≥ 80 years	16	15	19.5 (-38.0, 74.0)
Sex			
Male	78	95	8.0 (-12.0, 30.0)
Female	85	68	34.0 (12.0, 57.0)
Baseline 6MWD Category			
≤ 350 meters	136	133	24.0 (6.0, 41.0)
> 350 meters	27	30	16.0 (-16.0, 47.0)
PH-ILD Etiology			
Idiopathic Interstitial Pneumonia	65	81	32.0 (12.0, 55.0)
Combined Pulmonary Fibrosis and Emphysema	42	40	2.0 (-28.0, 32.0)
Connective Tissue Disease	40	32	39.0 (3.0, 78.0)
Other	16	10	0.0 (-89.0, 54.0)
Baseline PVR Category			
< 4 Wood units	32	34	-3.0 (-26.0, 26.0)
≥ 4 Wood units	131	129	28.0 (11.0, 46.0)
Study Drug Dose at Week 16			
4-6 breaths	6	2	-16.5 (-62.0, 29.0)
7-9 breaths	37	24	18.0 (-8.0, 43.0)
10-12 breaths	78	94	30.0 (14.0, 48.0)

6MWD, 6-minute walk distance; CI, confidence interval; H-L, Hodges-Lehmann; ILD, interstitial lung disease; LOCF, last observation carried forward; PH, pulmonary hypertension; PVR, pulmonary vascular resistance

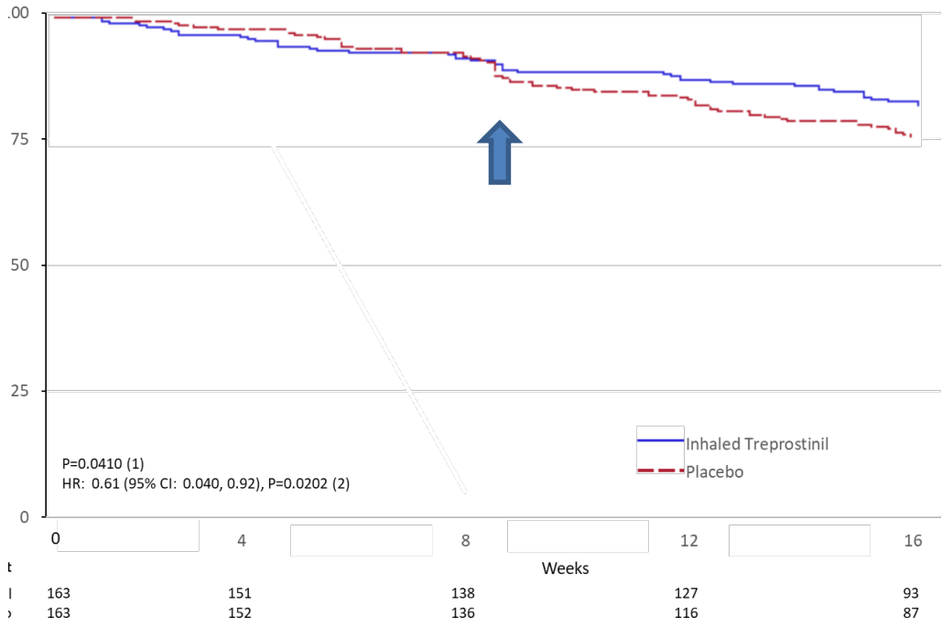
NT-proBNP Results by Study Visit



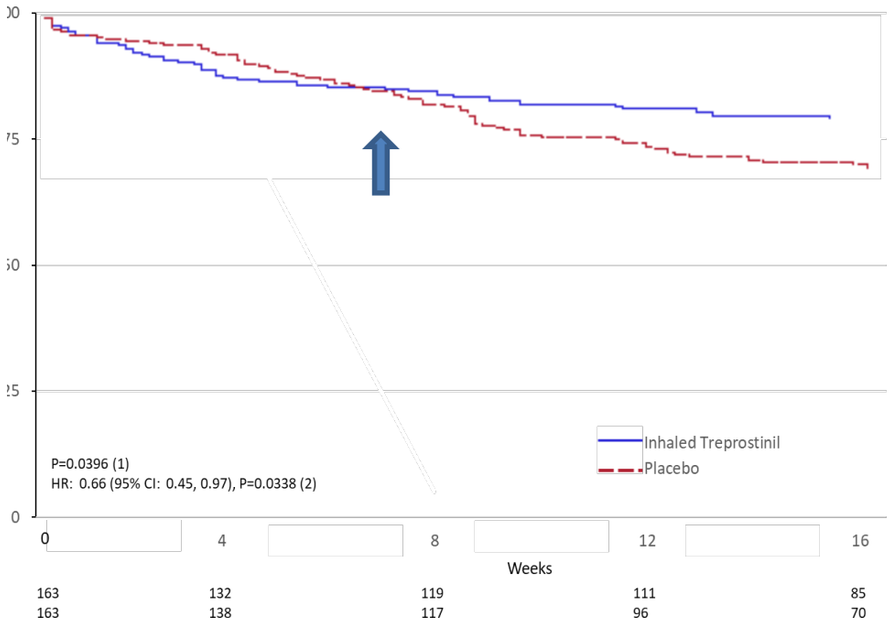
Inhaled treprostinil resulted in a 42% reduction in NT-proBNP when compared to placebo at Week 16 (P<0.001)

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.

Time to Exacerbation of Underlying Lung Disease



Time to Clinical Worsening Events

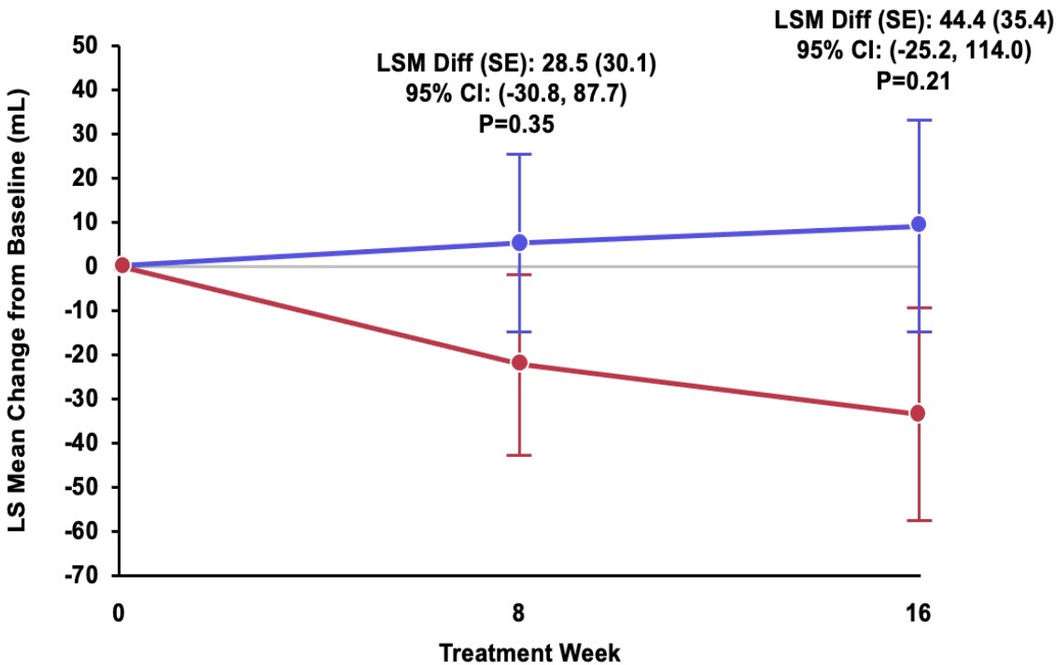


Exacerbation: acute, clinically significant, respiratory deterioration characterized by evidence of new widespread alveolar abnormality

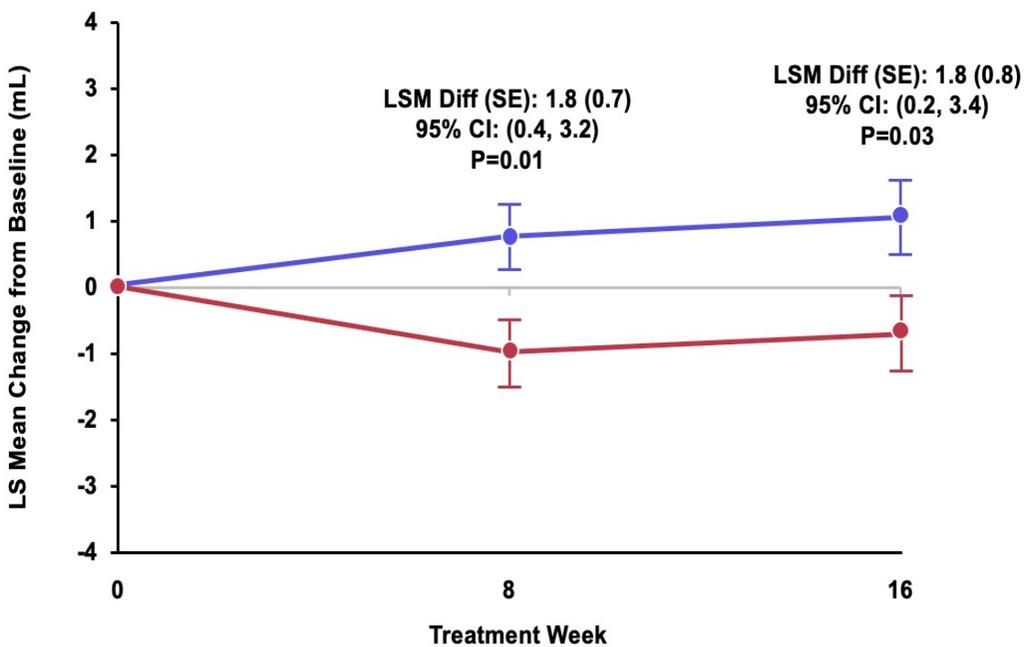
TTCW: death, need for and/or worsening-related listing for lung and/or heart transplant, need to initiate an approved PAH SOC rescue therapy, PAH-specific hospitalization, or functional deterioration (worsened WHO Functional Class AND 15% decrease in 6MWD)

FVC improved with inhaled treprostinil by 28.47 mL and 44.40 mL at Weeks 8 and 16, respectively, when compared to placebo

LS mean change in FVC (mL) by week for overall ITT population

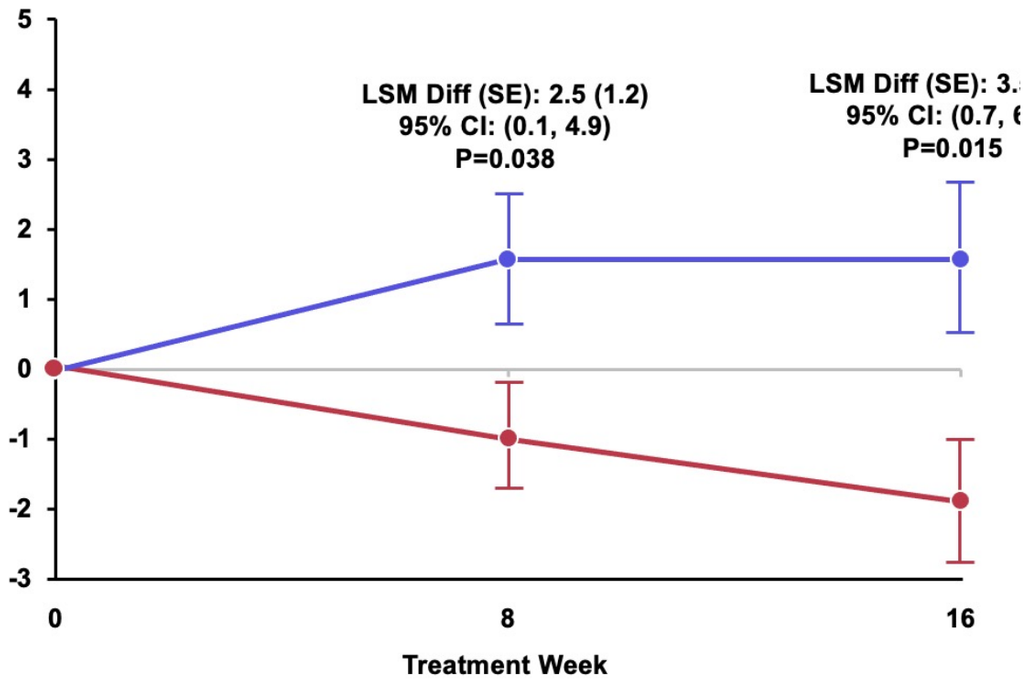


LS mean change in FVC % predicted by week for overall ITT population

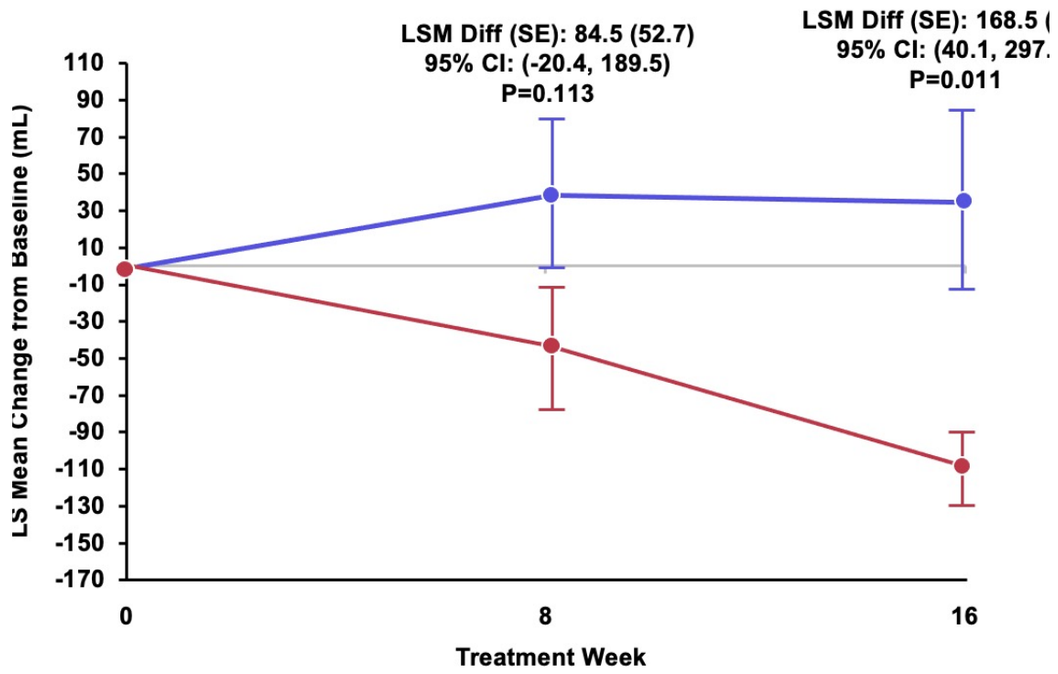


For patients with IPF FVC improvements of 84.52 mL and 168.52 mL (N=92, p=0.0108) at Weeks 8 and 16

LS mean change in FVC (mL) by week for subset of patients with IPF



LS mean change in FVC % predicted by week for subset of patients with IPF



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.

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Conclusions

- Findings of a significant placebo-corrected difference in:
  - FVC
  - Significantly fewer exacerbations
  - Patients on inhaled treprostinil had a favorable impact on the course of the underlying lung disease
- Along with preclinical evidence* demonstrating the antifibrotic activity of treprostinil this suggests that inhaled treprostinil may offer a treatment option for patients with ILD.
- Results support an additional treatment avenue and might herald a shift in the clinical management of patients with ILD.

*Sci Rep. 2018;8(1):1087; Pulm Circ. 2019;9(4):2045894019881954The Lancet Respir Med. 2021 Jun 29:S2213-2600

Conclusions

- PH exhibits a complex pathogenesis
- Improved outcomes, but long way to go
- Clear rational for combination therapy
- Clear benefit to treating patients with interstitial lung disease and pulmonary hypertension
- Room for additional therapeutic targets

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