Pulmonary Hypertension associated with Interstitial Lung Disease (PH-ILD)

KOL Day Presentation

Bellerophon Therapeutics I May 29, 2019

Bellerophon THERAPEUTICS

Forward Looking Statements

This presentation contains forward-looking statements that involve substantial risks and uncertainties. All statements, other than statements of historical facts, contained in this presentation, including statements regarding our strategy, future operations, future financial position, future revenues, projected costs, prospects, plans and objectives of management, are forward-looking statements. The words “anticipate,” “believe,” “estimate,” “expect,” “intend,” “may,” “plan,” “predict,” “project,” “target,” “potential,” “will,” “would,” “could,” “should,” “continue,” and similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words. We may not actually achieve the plans, intentions or expectations disclosed in our forward-looking statements, and you should not place undue reliance on our forward-looking statements. Actual results or events could differ materially from the plans, intentions and expectations disclosed in the forward-looking statements we make due to a number of important factors, including risks and uncertainties relating to: the timing and outcomes of our ongoing and expected clinical trials for our product candidates; our ability to successfully develop, commercialize and market any of our product candidates; our ability to obtain, maintain and enforce intellectual property rights; competition; our reliance on third parties; our ability to obtain necessary financing; and those risk factors discussed in the “Risk Factors” section and elsewhere in our most recent Form 10-K and other periodic filings we make with the SEC.

All forward-looking statements contained in this presentation reflect our current views with respect to future events. We assume no obligation, except as required by applicable law, to update any forward-looking statements publicly, or to update the reasons why actual results could differ materially from those anticipated in the forward-looking statements, even if new information becomes available in the future.

Agenda

Topic	Presenter
Bellerophon Corporate Highlights	**Fabian Tenenbaum** Chief Executive Officer Bellerophon Therapeutics
Pulmonary Hypertension associated with Interstitial Lung Disease *Disease Background and Current Treatment Landscape*	**Steven Nathan, M.D., FCCP** Medical Director, Advanced Lung Disease & Lung Transplant Program Inova Fairfax Hospital
Bellerophon Clinical Update	**Hunter Gillies, M.D.** Chief Medical Officer Bellerophon Therapeutics
Q & A	**Steven Nathan MD – Inova Fairfax Hospital** **Bellerophon Executive Team**

Bellerophon Therapeutics Corporate Highlights

Fabian Tenenbaum
Chief Executive Officer
Bellerophon Therapeutics

Bellerophon THERAPEUTICS

Bellerophon Therapeutics (BLPH)

Company Profile

Clinical-Stage Biotherapeutics Company	• Focused on developing inhaled nitric oxide (iNO) based therapies for outpatient management of chronic cardiopulmonary diseases • Portable, lightweight delivery system allows for chronic home use • Company spun-off from Ikaria
Novel Therapy Addressing Unmet Medical Needs	• Multiple late stage programs in pulmonary hypertension associated with underlying lung disease (WHO Group 3 & WHO Group 5) • Novel targeted vasodilation provides potential for first approved therapy in intended indications • Simplified regulatory approval pathway via existing nitric oxide NDA • Patent portfolio extends through 2039 as well as potential for 7-10 years of orphan exclusivity
Financial Summary	• Cash & Equivalents: $20.7M(1), No Debt(1) • Shares Outstanding = 68.9 million(1); Fully Diluted = 110.2 million(1)

Notes: (1) As of March 31, 2019 per Quarterly Report on Form 10-Q filed May 9, 2019

Development Pipeline

Indication	Market	Development Stage		
		2018	2019	2020
PH-ILD (WHO Group 3)	220,000 with ILD in US 35-40% with associated PH Unmet medical need $2B+ potential market	iNO-PF Phase 2b Cohort 1	iNO-PF Phase 2b Cohort 2	iNO-PF Phase 3 Cohort 3
PH-COPD (WHO Group 3)	12.7 million COPD in US ~27% with associate PH Unmet medical need Multi billion dollar potential market			PH-COPD Phase 2b
PH-Sarc (WHO Group 5)	200,000 with sarcoidosis in US Up to 30% with associated PH Unmet medical need $1B+ potential market		PH-Sarc Phase 2	

Key Milestones

Phase 2a Trial completed
Results presented in May 2017

Seamless Phase 2/3 iNO-PF Trial
Positive Cohort 1 results presented in Jan 2019
Cohort 2 completed in 2H2019
Phase 3 Cohort initiated in 1Q2020

Phase 2a Trial completed
Trial completed in Sept 2017

Phase 2b Trial: iNO-COPD
Trial design finalized

Phase 2 Trial
Initiated in 1Q2019

Pulmonary Hypertension associated with Interstitial Lung Disease
Disease Background and Current Treatment Landscape

Steven Nathan, M.D., FCCP

Medical Director, Advanced Lung Disease & Lung Transplant Program

Inova Fairfax Hospital

Bellerophon THERAPEUTICS

Pulsed Inhaled NO in Patients with Interstitial Lung Disease: just say “yes”?

Steven Nathan, MD, FCCP
Medical Director, Advanced Lung Disease & Lung Transplant Program
Inova Fairfax Hospital
Falls Church, VA

Disclosures

Steven Nathan, MD

Personal financial relationships with commercial interests relevant to this presentation during the past 12 months:

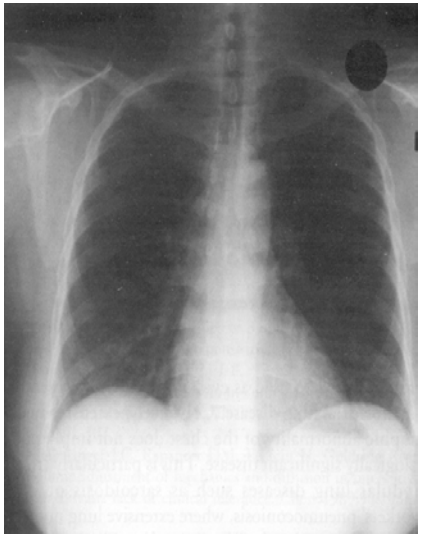
- **Consultant:** Bayer, Bellerophon, Boerhinger-Ingelheim, Galapagos, Gilead, Genentech-Roche, Promedior, Pliant, United Therapeutics, Veracyte.

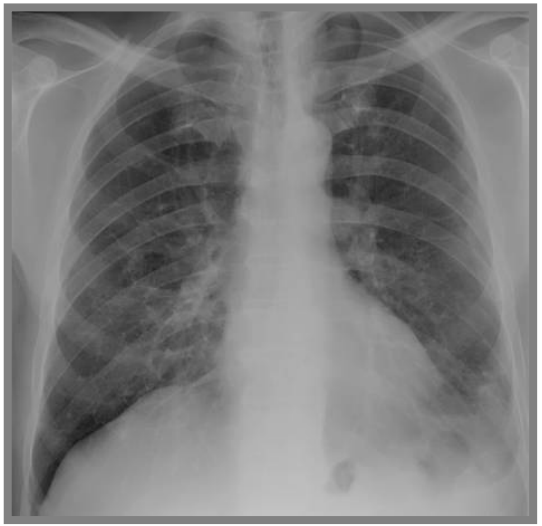
- **Speaker's Bureau:** Bayer, Boerhinger-Ingelheim, Genentech-Roche, Gilead, United Therapeutics.

- **Research Funding:** Bayer, Boerhinger-Ingelheim, Gilead, Genentech-Roche, United Therapeutics, Veracyte.

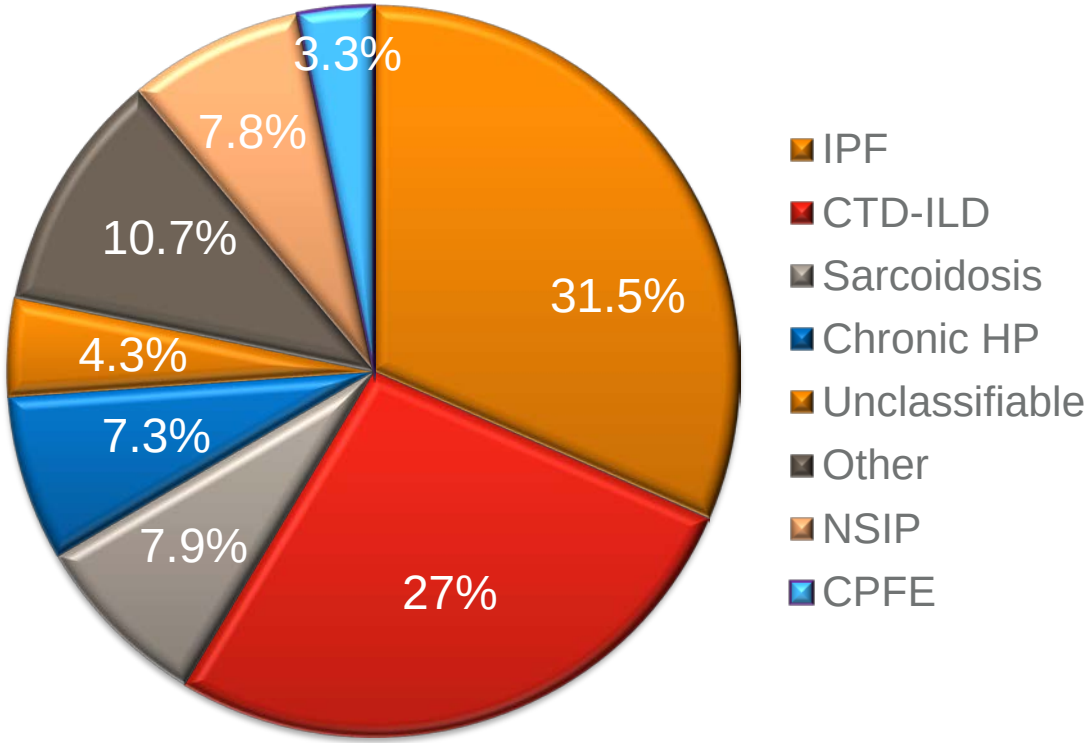
Interstitial lung disease is commonly confused with *Pulmonary Fibrosis* is commonly confused with *IPF*

Interstitial Lung Disease: A broad category of diffuse lung disease involving the interstitium of the lung characterized by variable amounts of inflammation and fibrosis



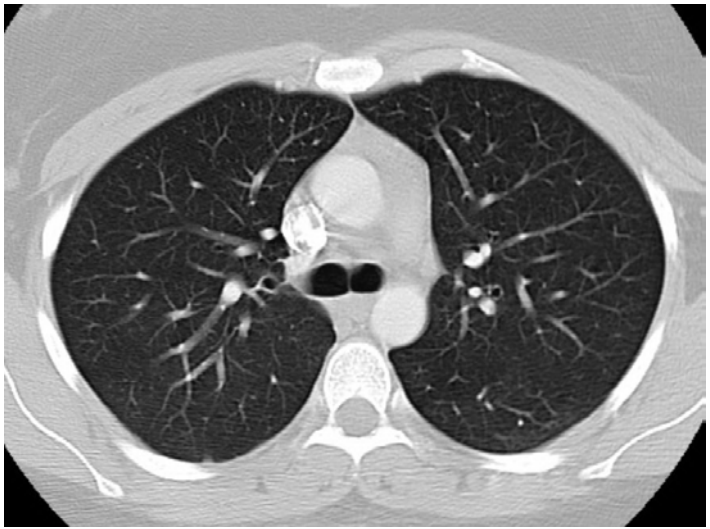


Spectrum of ILD followed by the Inova Advanced Lung Disease Program (2018)

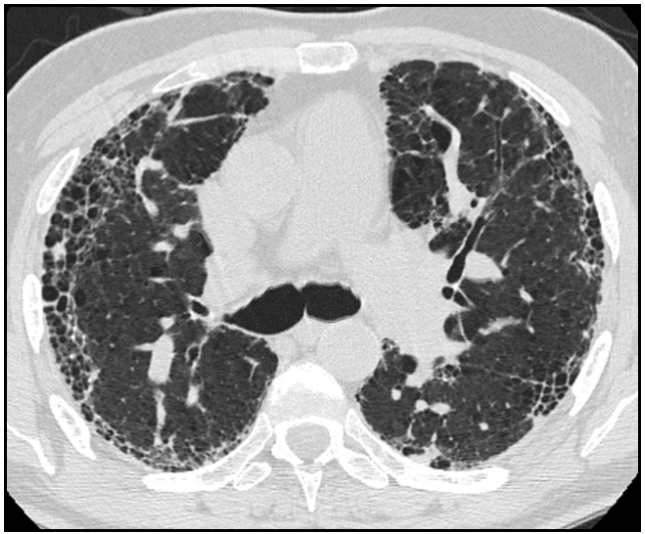


CT of the Chest is the Main Diagnostic Tool

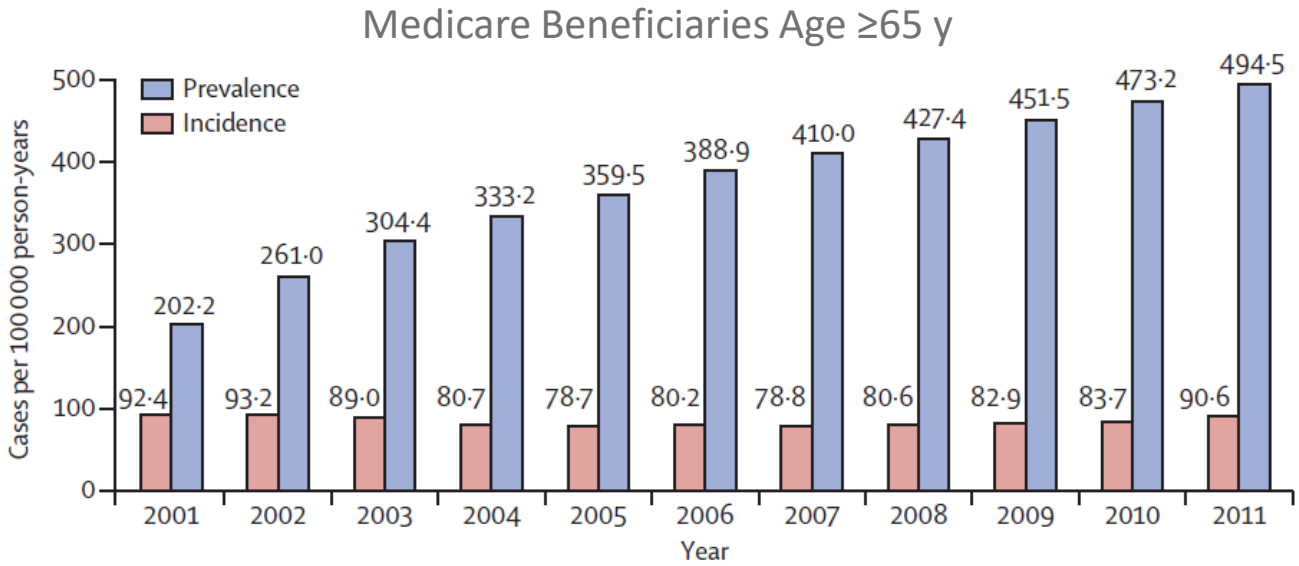
NORMAL



IPF



Increasing Prevalence of IPF



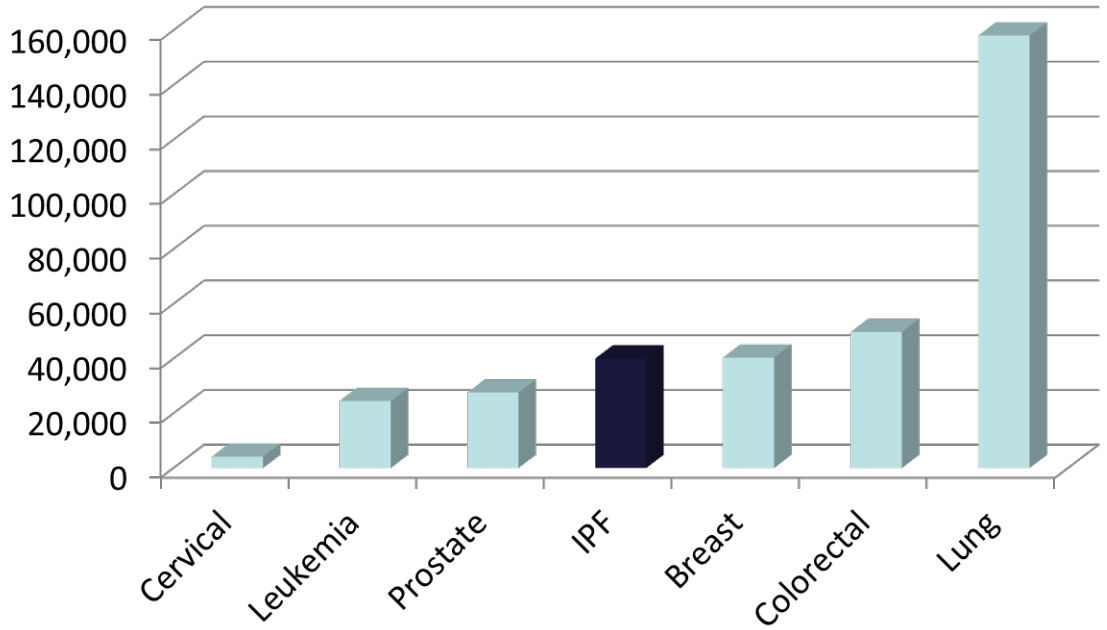
Factors associated with lower survival

- Age, index year, male gender

Median survival = 3.8 y

1. Raghu G et al. *Lancet Respir Med*. 2014;2:566-572

Estimated Deaths: IPF[1] vs Common Cancers[2]

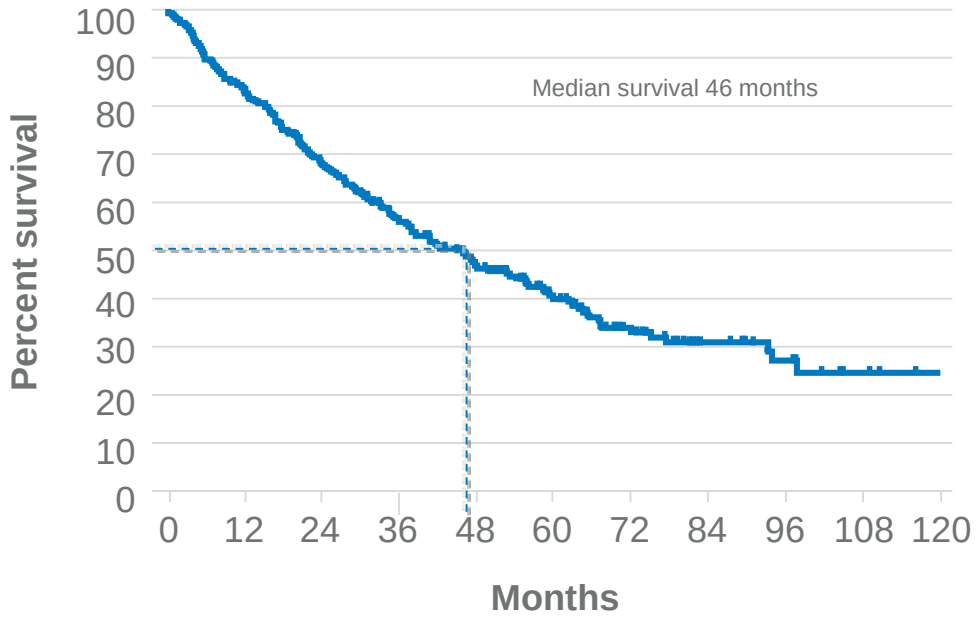


1. Coalition for Pulmonary Fibrosis. Facts About Idiopathic Pulmonary Fibrosis. Available at: http://www.coalitionforpf.org/facts-about-idiopathic-pulmonary-fibrosis/.
2. American Cancer Society, Surveillance and Health Services Research, 2015. Available at: http://www.cancer.org/acs/groups/content/@editorial/documents/document/acspc-044552.pdf.

How Do IPF Patients Present?

- Shortness of breath (dyspnea)
- Dry cough
- Fatigue
- Exercise desaturation
- “Velcro” rales at lung bases
- Clubbing of fingers and/or toes may be present
- Incidentally
  - ILD on routine CXR or CT chest
  - ILD at bases of abdominal CT
  - Fluoroscopy at time of cardiac catheterization
  - Family history

Idiopathic Pulmonary Fibrosis: the prototypical pulmonary fibrotic disorder
Survival in the pre-antifibrotic era 2000–2009 (N=357)

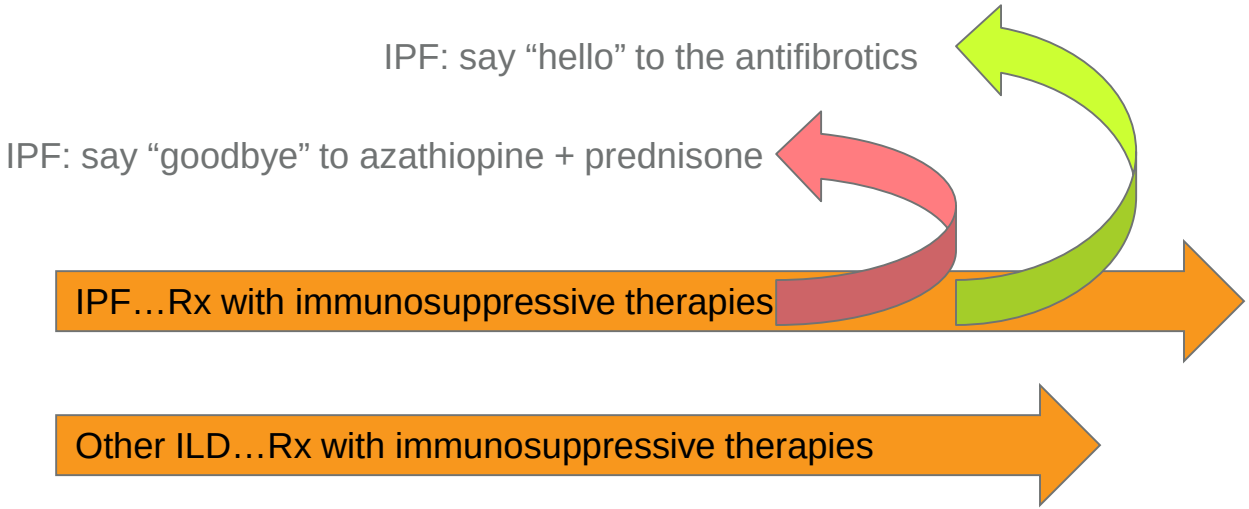


Lung transplant recipients were excluded from these analyses
RXUKESBR00231ak/Date of preparation: May 2017

Nathan SD, et al. *Chest.* 2011;140:221–229

Seismic Treatment Paradigm Shift

IPF, IIPs and CTD-ILD= historic parallel treatment paths

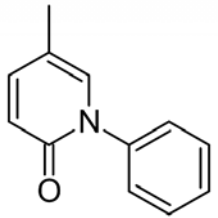


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Phase 3 Trial of Pirfenidone in Patients with Idiopathic Pulmonary Fibrosis

Talmadge E. King, Jr., M.D., Williamson Z. Bradford, M.D., Ph.D., Socorro Castro-Bernardini, M.D., Elizabeth A. Fagan, M.D., Ian Glaspole, M.B., B.S., Ph.D., Marilyn K. Glassberg, M.D., Eduard Gorina, M.D., Peter M. Hopkins, M.D., David Kardatzke, Ph.D., Lisa Lancaster, M.D., David J. Lederer, M.D., Steven D. Nathan, M.D., Carlos A. Pereira, M.D., Steven A. Sahn, M.D., Robert Sussman, M.D., Jeffrey J. Swigris, D.O., and Paul W. Noble, M.D., for the ASCEND Study Group*



King TE Jr., et al. *N Engl J Med*. 2014;370:2083-2092.

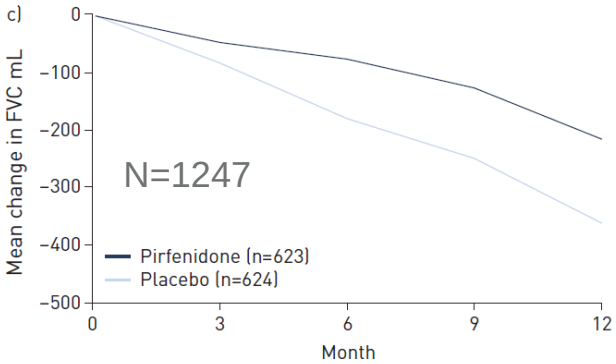
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 29, 2014 VOL. 370 NO. 22

Efficacy and Safety of Nintedanib in Idiopathic Pulmonary Fibrosis

Luca Richeldi, M.D., Ph.D., Roland M. du Bois, M.D., Ganesh Raghu, M.D., Arata Azuma, M.D., Ph.D., Kevin K. Brown, M.D., Ulrich Costabel, M.D., Vincent Cottin, M.D., Ph.D., Kevin R. Flaherty, M.D., David M. Hansell, M.D., Yoshikazu Inoue, M.D., Ph.D., Dong Soon Kim, M.D., Martin Kolb, M.D., Ph.D., Andrew G. Nicholson, D.M., Paul W. Noble, M.D., Moisés Selman, M.D., Hiroyuki Taniguchi, M.D., Ph.D., Michèle Brun, M.Sc., Florence Le Maulf, M.Sc., Mannaïg Girard, M.Sc., Susanne Stowasser, M.D., Rozsa Schlenker-Herceg, M.D., Bernd Disse, M.D., Ph.D., and Harold R. Collard, M.D., for the INPULSIS Trial Investigators*

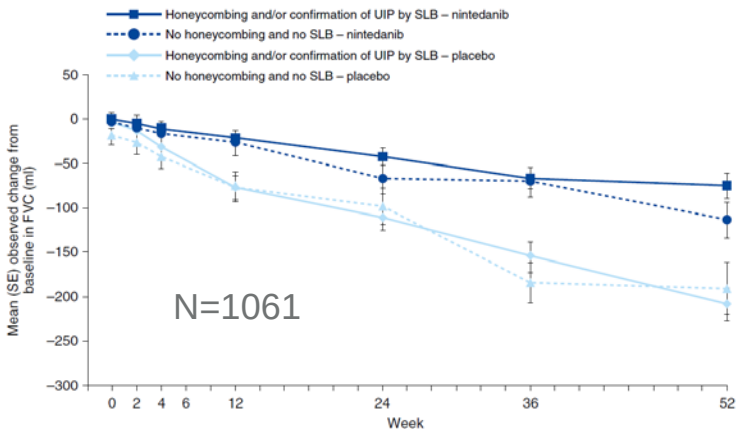
Antifibrotics approved based on slowing of loss of FVC



Absolute difference mL	36	104	123	148
Relative difference %	43.5	57.3	49.1	40.7
Rank ANCOVA p-value	<0.001	<0.001	<0.001	<0.001

PIRFENIDONE

Eur Respir J 2016; 47: 27–30



NINTEDANIB

Am J Respir Crit Care Med Vol 195, Iss 1, pp 78–85, Jan 1, 2017

Approved Antifibrotic Therapies for Patients with IPF

Pirfenidone

- FDA approval 2014
- Anti-fibrotic properties; exact mechanism of action unknown
- Orally administered, 801 mg, 3 times daily
- Nausea, rash/sun sensitivity, dyspepsia/GERD

Nintedanib

- FDA approval 2014
- Tyrosine kinase inhibitor; targets FGFR, PDGFR, VEGFR, FLT3
- Orally administered, 150 mg, 2 times daily
- Diarrhea, nausea

Galli JA, et al. *Respirology*. 2017;22:1171-1178.

Pirfenidone & Nintedanib: Clinical Trial Endpoints

Ascend (Pirfenidone)

Primary

- Change from baseline to week 52 in %FVC

Key Secondary endpoints

- Δ 6MWT distance at week 52
- Progression-free survival
  time to first event of either:
  -↓ 10% FVC,
  -↓50m 6MWT
  -death

Other secondary outcomes (n=3)

- All-cause mortality
- Treatment-emergent IPF-related mortality
- Δ UCSD SOBQ at 52 weeks

Inpulsis (Nintedanib)

Primary

- Annual rate of decline in FVC (expressed as ml/52 weeks)

Key Secondary endpoints

- ΔSGRQ over 52 weeks
- Time to 1st acute IPF exacerbation

Secondary endpoints (n=19)

- Respiratory mortality
- Overall survival
- On-treatment survival
- FVC analyses
  - Absolute and relative Δ at 52 weeks
  - Absolute categorical Δ at 52 weeks (by 5 and 10%)
- Risk ratio of IPF AE

More next slide

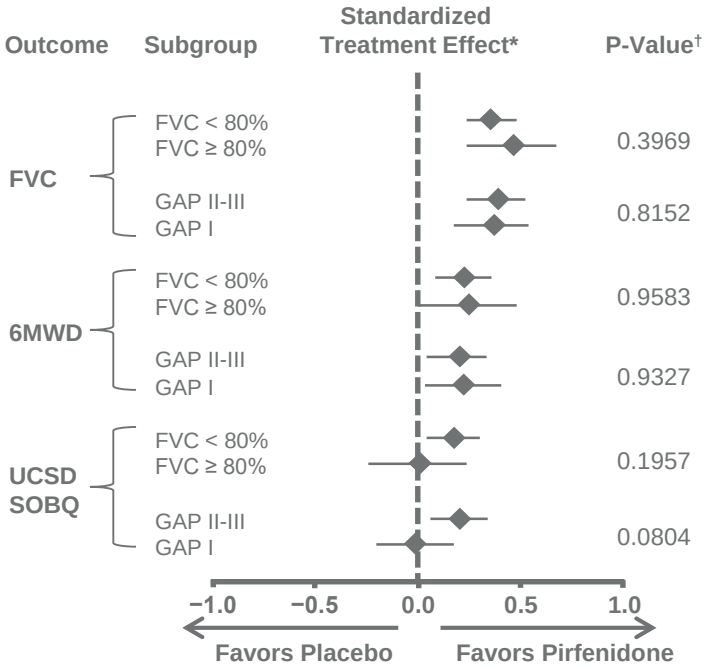
Endpoints

Inpulsis (Nintedanib)

Secondary endpoints (continued)

- PROs
  - SGRQ (three analyses)
  - SOBQ
  - CASA-Q
  - PGI-C
  - EQ-5D
- Time to death or lung transplant
- Time to death or lung transplant or qualifying for lung transplant
- ΔSpO2 at 52 weeks
- ΔDLco at 52 weeks

Does disease severity matter in detecting differences in outcomes ?

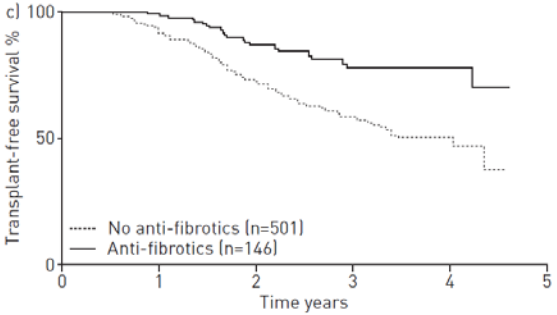


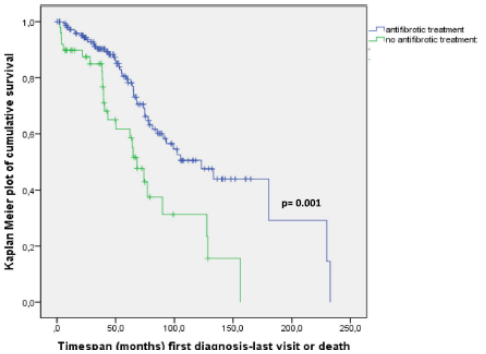
Pirfenidone associated with decreases in the proportions of patients experiencing categorical declines in the three outcomes with **no significant differences** between mild and moderate disease

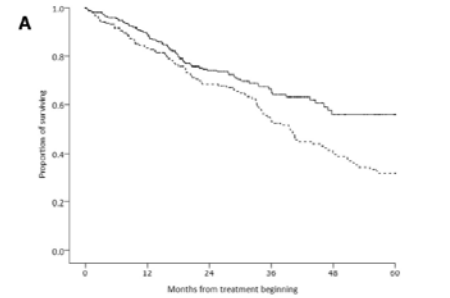
* For FVC and 6MWD: treatment difference = pirfenidone – placebo; for UCSD SOBQ, treatment difference = placebo – pirfenidone.
6MWD, 6-minute walk distance; FVC, forced vital capacity; UCSD SOBQ, University of California—San Diego Shortness of Breath Questionnaire.
† The P-value is from the test statistic for testing the interaction between the treatment and subgroup variable.

Carlo Albera et al. Eur Respir J July 2016. doi:10.1183/13993003.01966-2015

Registry Data: survival on & off antifibrotic Rx







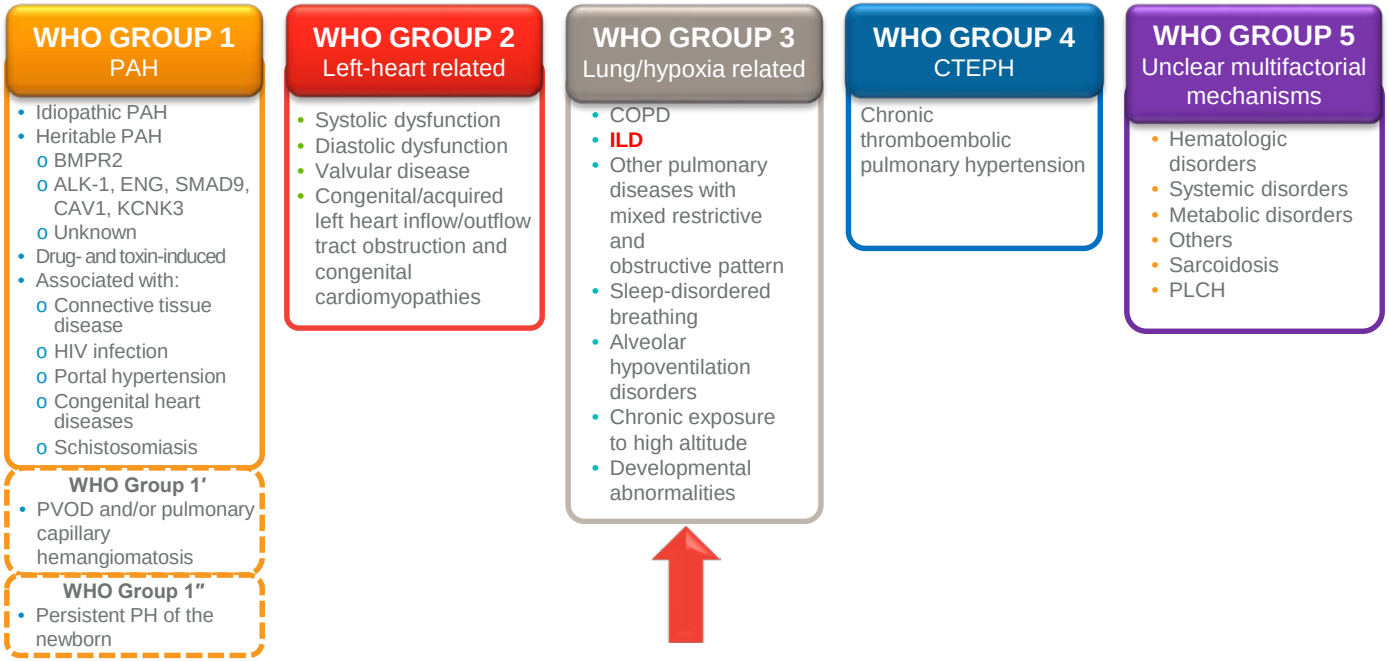
	12-moOS (95% CI)	24-mo OS (95% CI)	60-mo OS (95% CI)	p (LogRank)
Pirfenidone	0.888 (0.855; 0.922)	0.742 (0.690; 0.793)	0.559 (0.474; 0.644)	0.002
No-antifibrotic treatment	0.833 (0.780; 0.886)	0.684 (0.613; 0.754)	0.315 (0.234; 0.396)	

Jo et al. Eur Respir J 2017;49:1601592

Guenther et al. Respiratory Research 2018;19:141

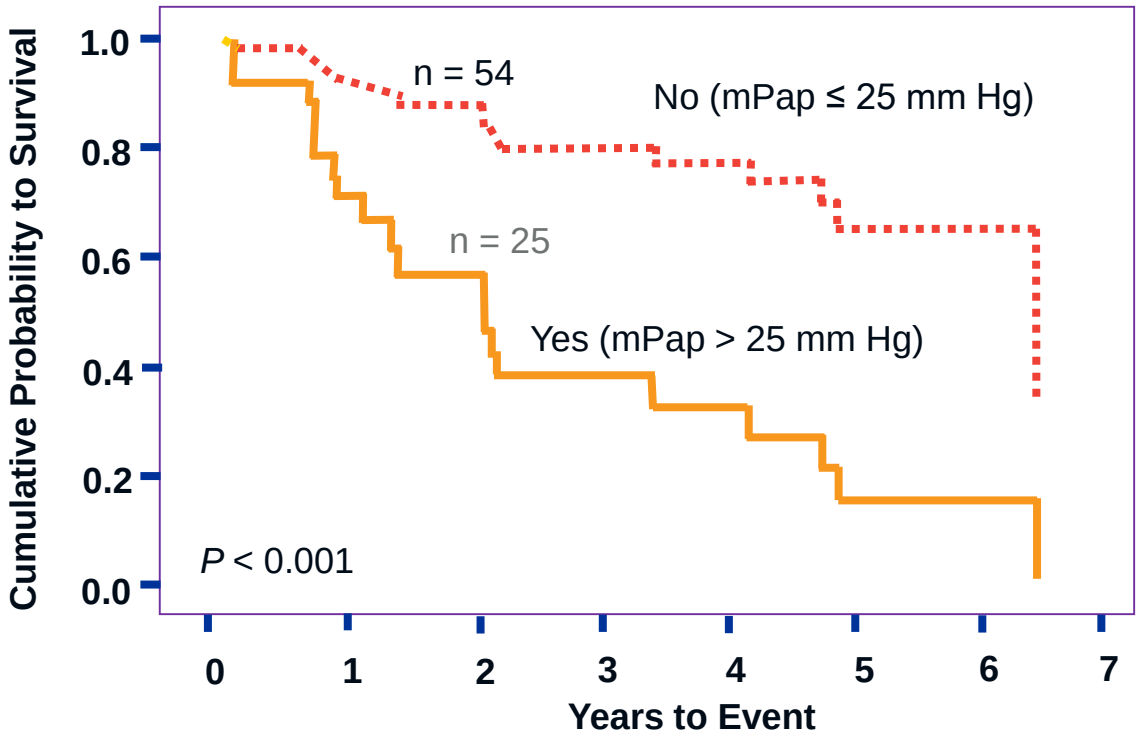
Zurkova et al. Respiratory Research (2019) 20:16

Clinical Classification of Pulmonary Hypertension



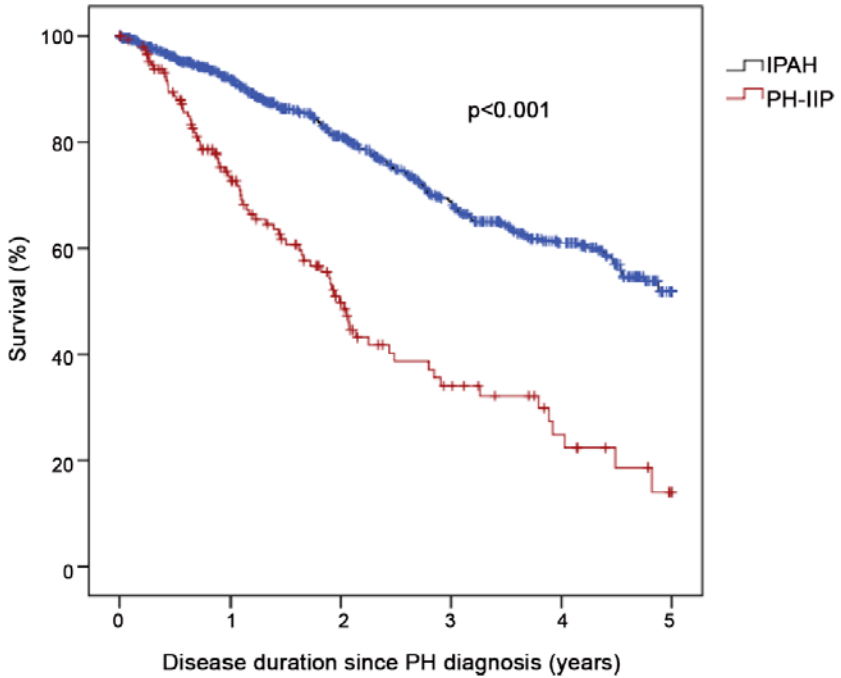
Simonneau G et al. *J Am Coll Cardiol*. 2013;62(suppl):D34-D41.

Mean Pulmonary Artery Pressure can Provide Prognostic Value in IPF



Chest. 2006;129:746-752.

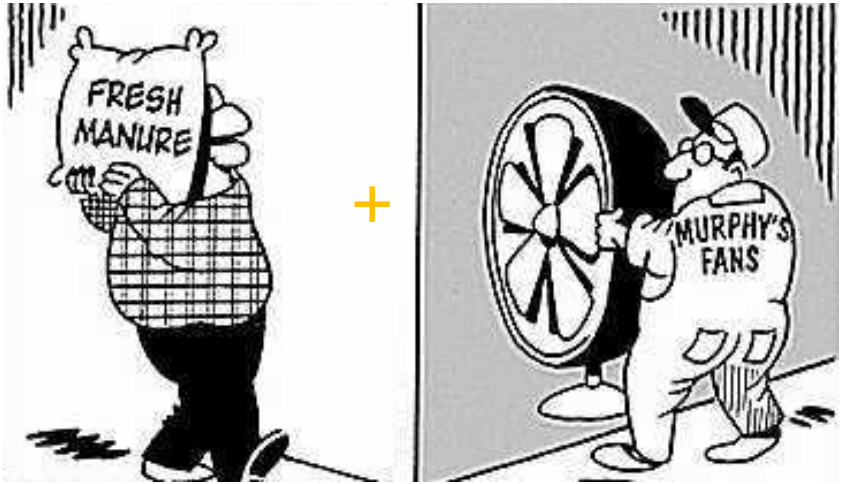
Survival Comparison:
Idiopathic Pulmonary Arterial Hypertension
vs
Pulmonary Fibrosis Complicated by Pulmonary Hypertension



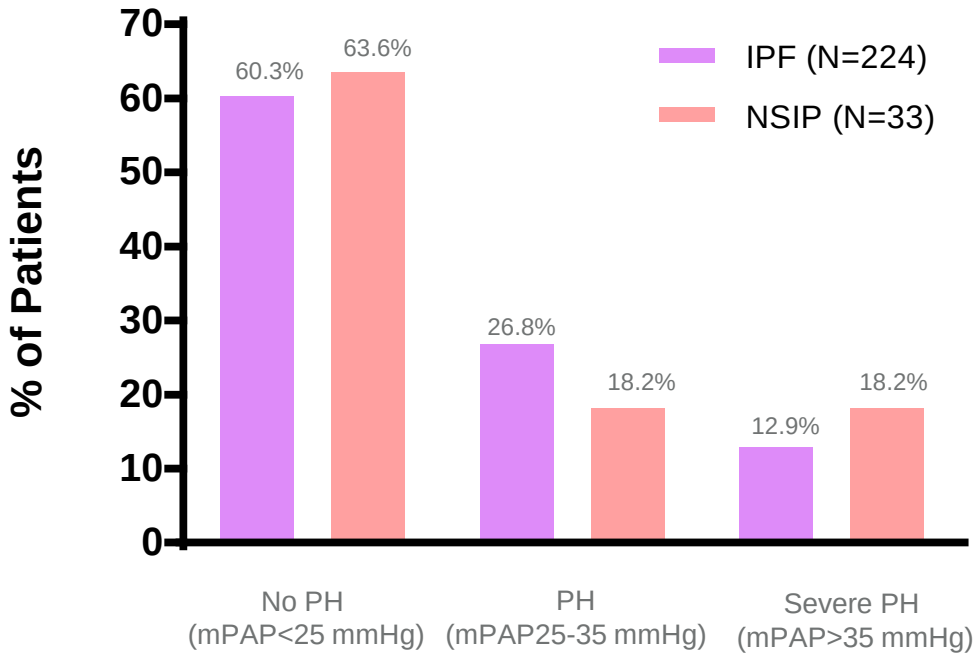
Hoeper et al. PLOS ONE | DOI:10.1371/journal.pone.0141911 December 2, 2015

What happens when you put 2 bad diseases together?

PF+PH=

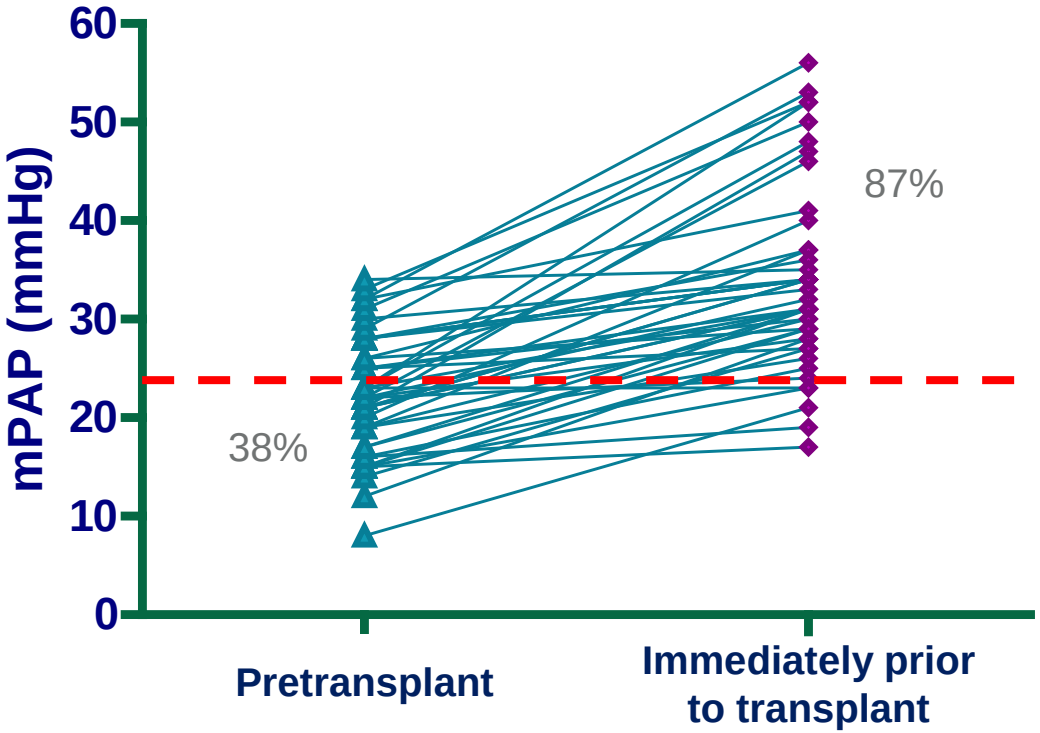


PH in Pulmonary Fibrosis & NSIP: Prevalence



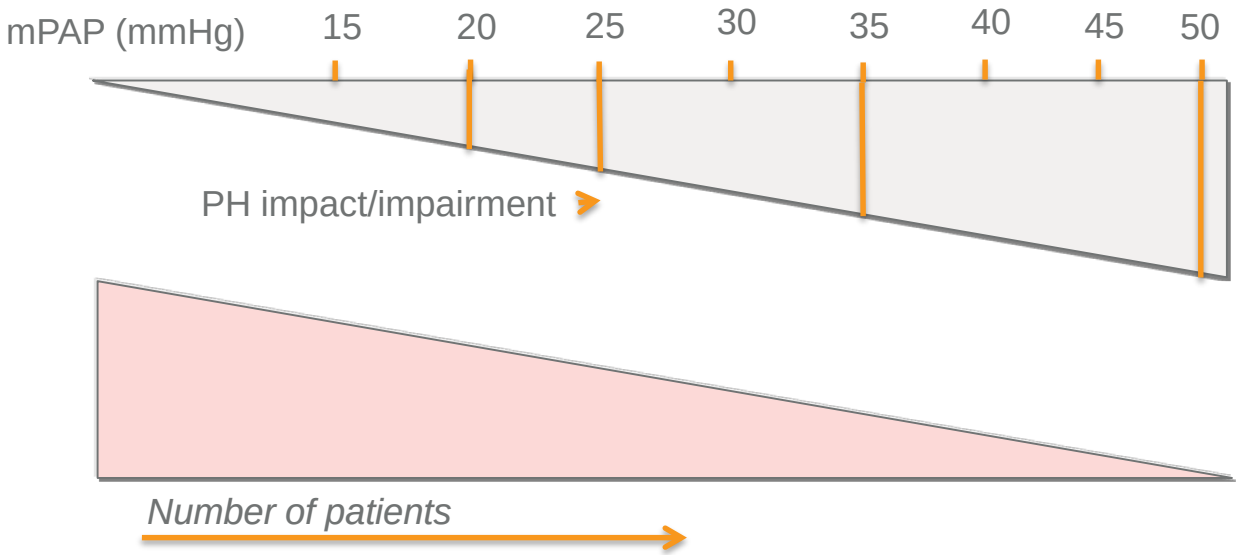
Inova Fairfax data: August 2013

PH Progression in IPF



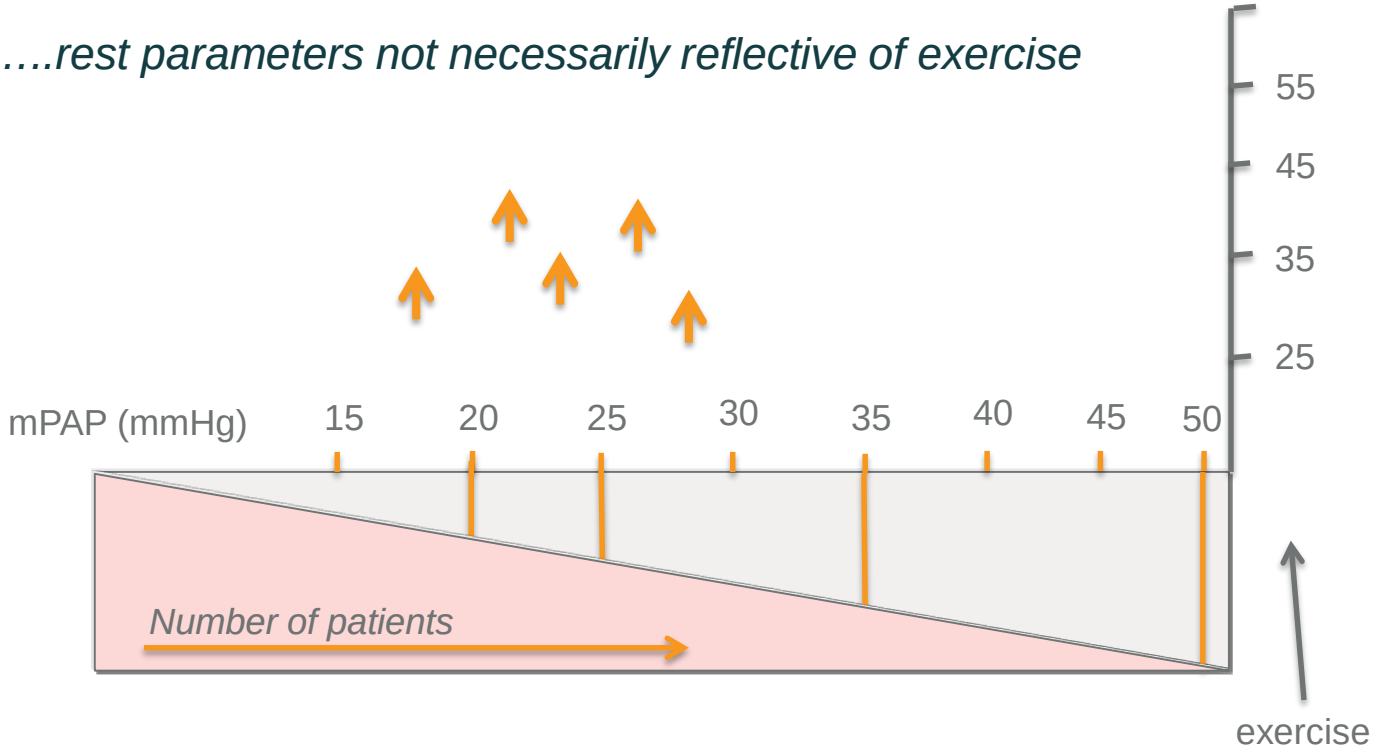
Respiration 2008;76:288-294

Pulmonary Vascular Involvement: A Spectrum and Continuum



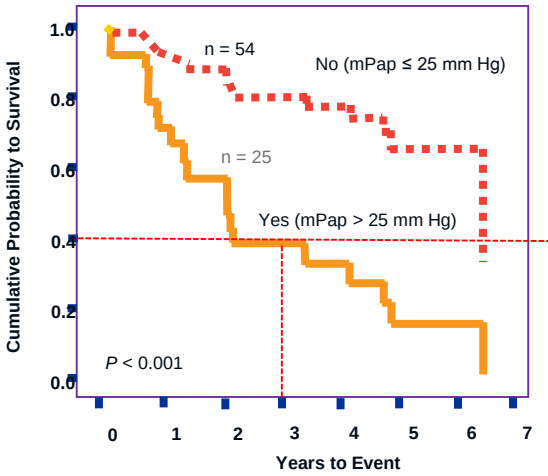
Pulmonary Vascular Involvement: A Spectrum and Continuum

…..rest parameters not necessarily reflective of exercise



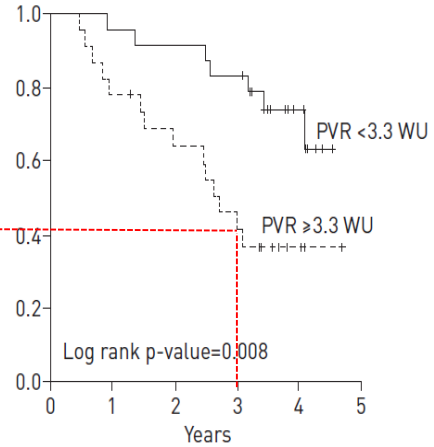
Presence of PH Associated with Worse Outcomes in ILD

IPF



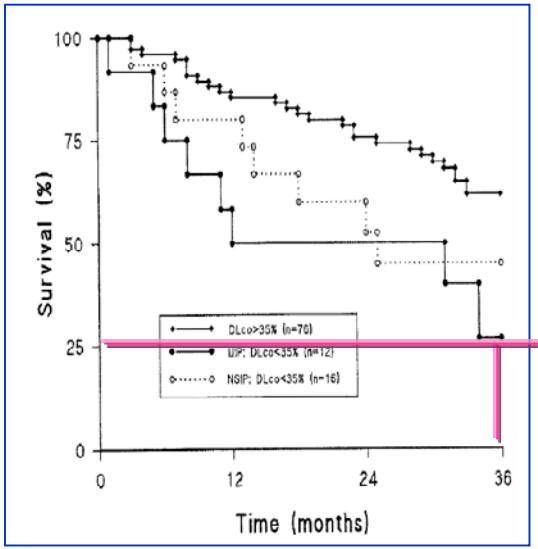
Chest. 2006;129:746-752.

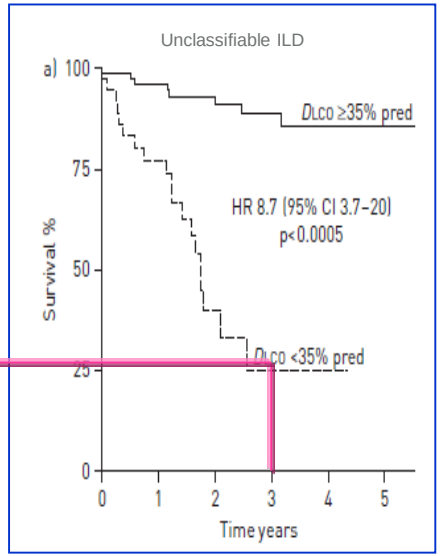
Chronic HP



Eur Respir J 2018; 51: 1800430.

Outcomes Are Similar in ILD's When Dlco<35%?





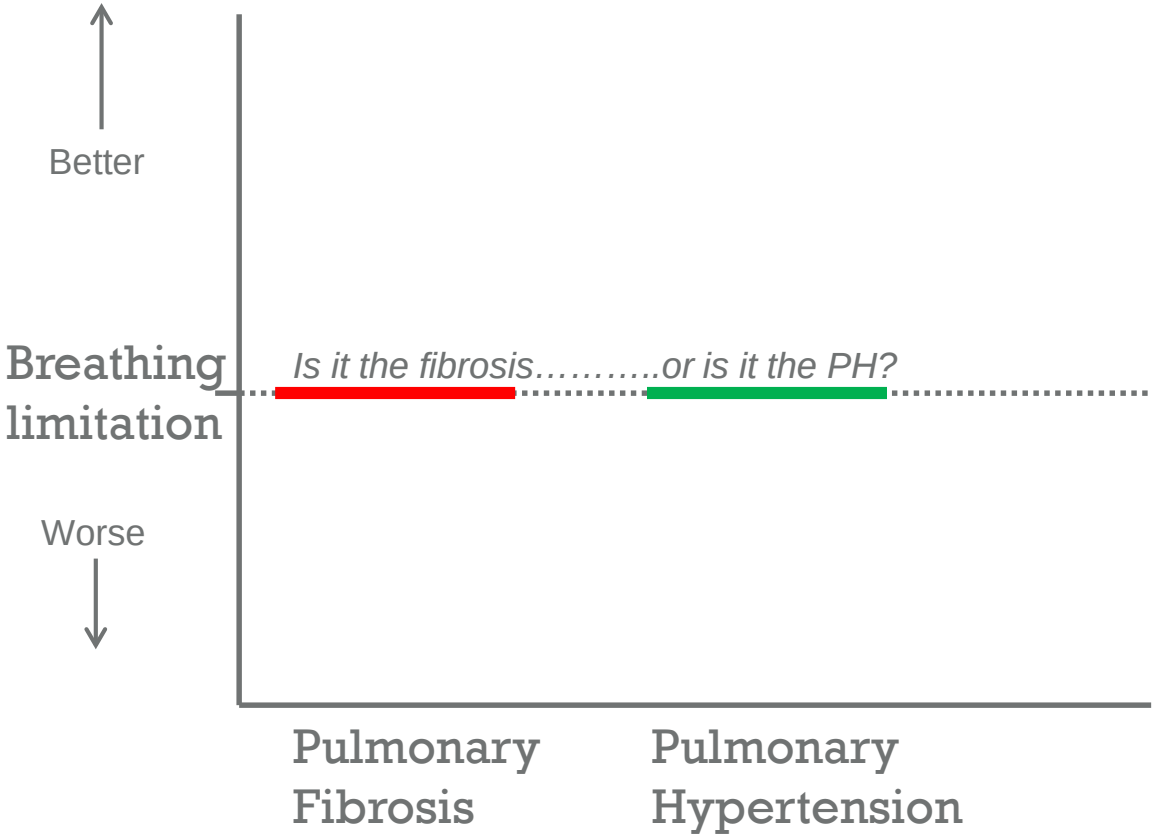
Am J Respir Crit Care Med 2003;168:531-537
Eur Respir J 2013;42:750-757

PH in IPF: Association with Desaturation and Reduced Distance on 6MWT

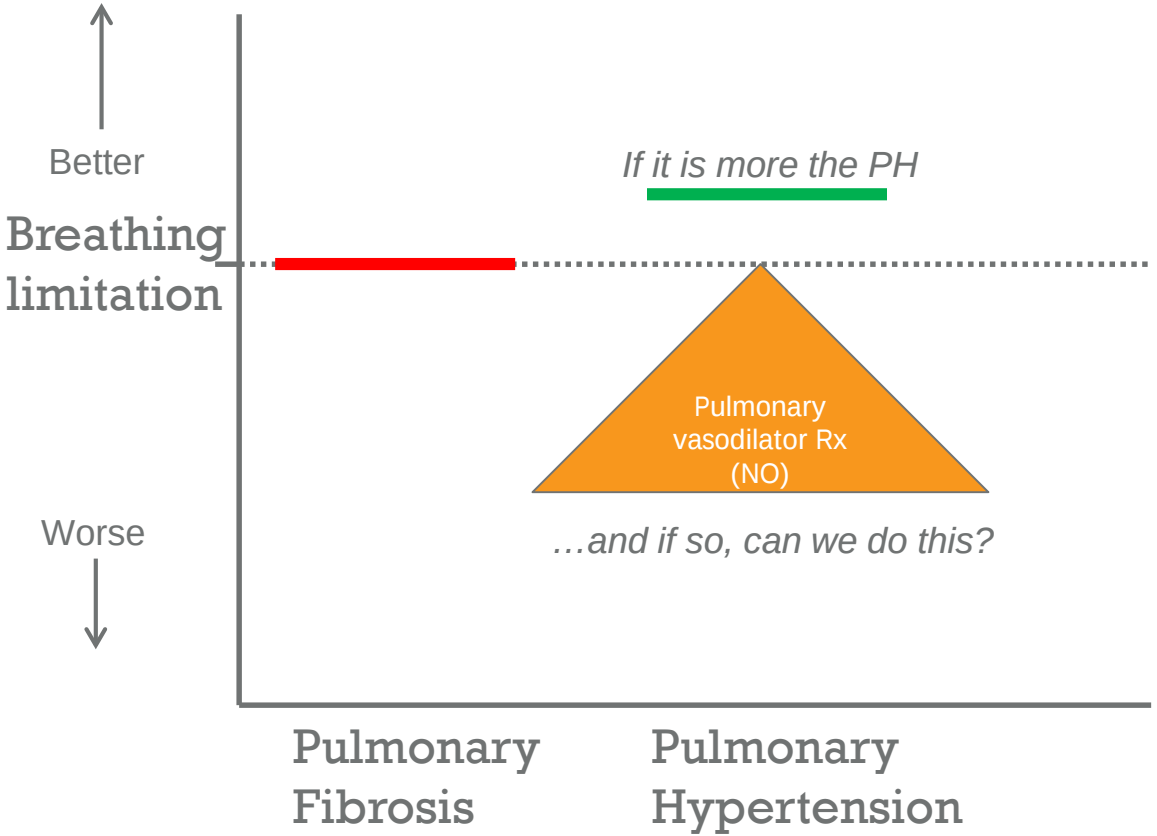
	mPAP ≤ 25 mm Hg (N=24)	mPAP > 25 mm Hg (N=10)	P value
6MWD (m)	366 ± 82	144 ± 66	<0.001
SpO2 Nadir (%)	88 ± 4	80 ± 4	<0.001

Lettieri et al. *Chest.* 2006;129:746-752.

Lung Disease and PH:
What is the limiting factor?

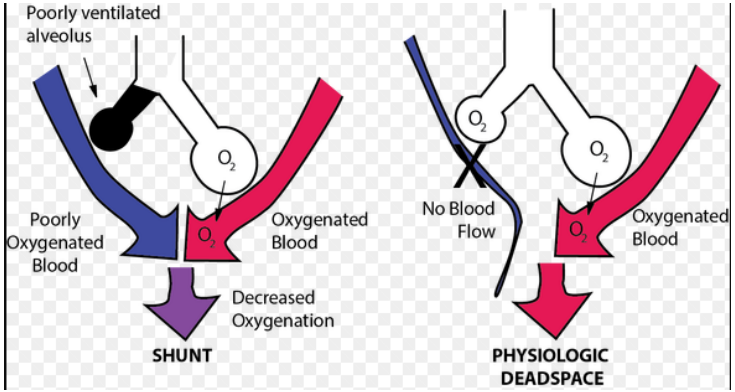


Lung Disease and PH:
What is the limiting factor?



Why pulsed iNO makes sense

- Local administration
- Very short-half-life
- Minimal systemic side-effects
- “Double dip” on chances of success
  - Ameliorate pulmonary hypertension
  - Improve ventilation perfusion matching



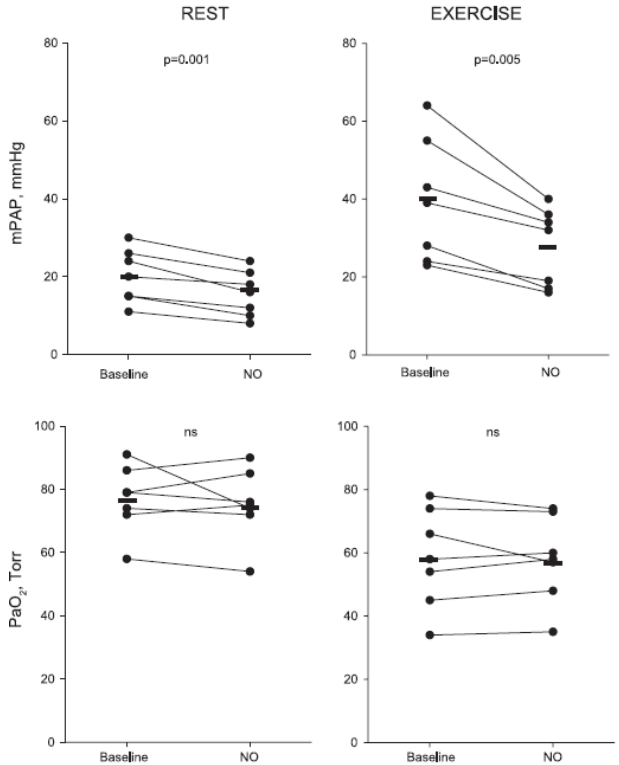
PH-PF Patients exhibit reduced levels of endogenous NO

Exhaled Nitric Oxide During Exercise in Primary Pulmonary Hypertension and Pulmonary Fibrosis*

Study objectives: Nitric oxide (NO), a potent vasodilator, is present in the exhaled air of humans. We wished to quantify NO production in patients with abnormalities of the pulmonary circulation.
Participants: Nine patients with primary pulmonary hypertension (PPH), six with pulmonary fibrosis (PF), and 20 normal volunteers were studied.
Interventions: All subjects were studied at rest and during continuous incremental (ramp) cycle ergometry exercise. All patients with PPH and nine matched normal volunteers also performed constant exercise at equal absolute work rates.
Measurements and results: The concentration of NO was measured continuously in mixed expired air, and the rate of NO production ($\dot{V}NO$) calculated. Peak exercise capacity was markedly impaired in both patient groups. $\dot{V}NO$ was similar at rest in the PPH patients (142±84 nL/min) and the normal subjects (117±45 nL/min), but lower in the PF patients (66±13 nL/min; $p<0.05$; analysis of variance with Bonferonni correction). While $\dot{V}NO$ in normal subjects more than doubled by peak exercise to 268±85 nL/min, there was no significant rise with exercise in either patient group (PPH, 155±81 nL/min; PF, 91±67 nL/min). Constant work rate exercise induced a significant rise in $\dot{V}NO$ in the normal subjects (*rest*, 101±68 nL/min; *exercise*, 147±87 nL/min; $p<0.001$) but no significant change in the PPH patients (*rest*, 127±111 nL/min; *exercise*, 68±65 nL/min).
Conclusions: We conclude that the low resting $\dot{V}NO$ in PF may be due to loss of normal functional pulmonary capillary bed. The increase in $\dot{V}NO$ seen in normal subjects may be associated with dilatation and recruitment of the pulmonary capillary bed during exercise, and failure to increase $\dot{V}NO$ during exercise in disease states may reflect an inability to recruit the capillary bed.

Chest 1997;111:44-50

Hemodynamic effects of NO at rest and with exercise in patients with IPF



J Appl Physiol 2011:638-645

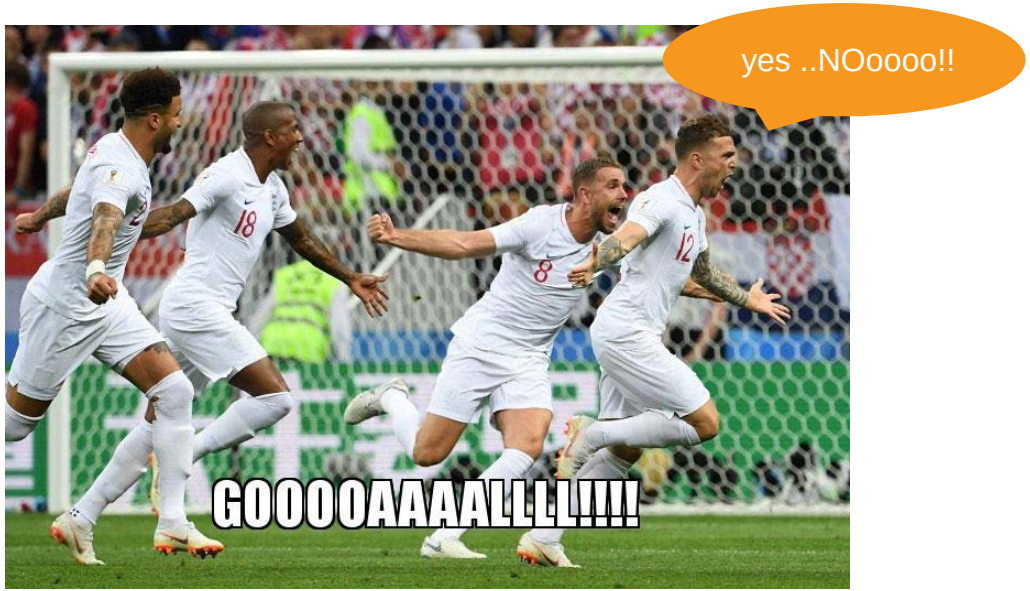
Outpatient Inhaled Nitric Oxide in a Patient With Idiopathic Pulmonary Fibrosis: A Bridge to Lung Transplantation

Gordon L. Yung, MB, BS,[a] Jolene M. Kriett, MD,[b]
Stuart W. Jamieson, MB, FRCS,[b] F. Wayne Johnson, RPFT, RCP,[c]
John Newhart, RCP,[c] Katie Kinninger, RCP,[c] Richard N. Channick, MD[a]

Inhaled nitric oxide (INO) has been shown to improve oxygenation and decrease intrapulmonary shunt and pulmonary hypertension in various lung diseases. In this study we report a patient with end-stage idiopathic pulmonary fibrosis and pulmonary hypertension who received INO after coronary artery bypass surgery, with significant improvement in arterial oxygenation and pulmonary arterial pressure. Using a pulsing delivery system, the patient continued to receive outpatient INO for 30 months while waiting for lung transplantation. Exercise study and two-dimensional echocardiogram, after 3 months of inhaled NO, demonstrated continued benefits of INO for improvement of arterial oxygenation, pulmonary arterial pressure and exercise tolerance. J Heart Lung Transplant 2001;20:1224–1227.

Inhaled NO affords us two shots on goal!

- Improved oxygenation
- Improved hemodynamics



HOW BEST TO SHOW THIS?

- “Comprehensive patient centric clinical outcomes preferable”
- IIP can be studied together with chronic HP and occupational lung disease.
- Studies employing inhaled therapies are an attractive option as this may enable better ventilation/perfusion matching and limit systemic side-effects

TABLE 3 Recommendations and questions for the future direction of research in chronic lung disease (CLD)-associated pulmonary hypertension (PH)

Development of better animal models of PH in both COPD and ILD encouraged
- Differential molecular mechanisms (parenchymal *versus* vascular)

- Nature, extent and spatial distribution of the parenchymal and vascular abnormalities

Optimal patient phenotype for trials of therapy
- Best haemodynamic variable(s) and threshold to define the patient phenotype; evaluation of right ventricular dysfunction for enrolment; extent of permissible parenchymal lung disease?
- Combination of pulmonary function testing, haemodynamic profile and imaging required

Clinical trial end-points in PH with underlying lung disease
- Phase 2 studies: physiological variables (*e.g.* right ventricular function, haemodynamics, 6MWT) and biomarkers (*e.g.* BNP) acceptable
- Phase 3 studies: comprehensive patient centric clinical outcomes preferable: composite end-point, time to clinically meaningful change (clinical worsening and/or improvement)
- Clinical worsening events may include: mortality, hospitalisation (cardiopulmonary), categorical changes in a functional test (*e.g.* 6MWT), QoL measures, NYHA Functional Class change, need for supplemental oxygen, disease exacerbation, lung transplantation

6MWT: improve its group 3 informative value ("integrate" distance, deoxygenation, Borg dyspnoea score, heart rate recovery?)

Encourage cardiopulmonary exercise testing for more elaborate distinction between respiratory *versus* circulatory limitation (problem: supplemental oxygen dependency)

Haemodynamic assessment while exercising is encouraged and is to be standardised

Inclusion spectrum in group 3 in view of different aetiology, molecular pathology and clinical course: "narrow *versus* broad"?

IIP can be studied together with chronic hypersensitivity pneumonitis and occupational lung disease

Sarcoidosis-PH sufficiently different and should be studied independently

COPD-PH should be studied independently

CPFE-PH included in ILD-PH studies; permissible provided the extent of their emphysema is not too great; or risk for confounding signal?

Studies employing inhaled PH therapies are an attractive option as this may enable better ventilation/perfusion matching and limit systemic side-effects

Future studies should focus on the prevention/inhibition/reversal of vascular remodelling in addition to vasodilation CLD-PH

Future studies should also target role of the vascular compartment in driving parenchymal abnormalities ("vascular therapy beyond PH")

Further studies of the role of pulmonary rehabilitation (exercise training) in lung disease complicated by PH are encouraged

Nathan et. al. Eur Respir J 2019; 53: 1801914

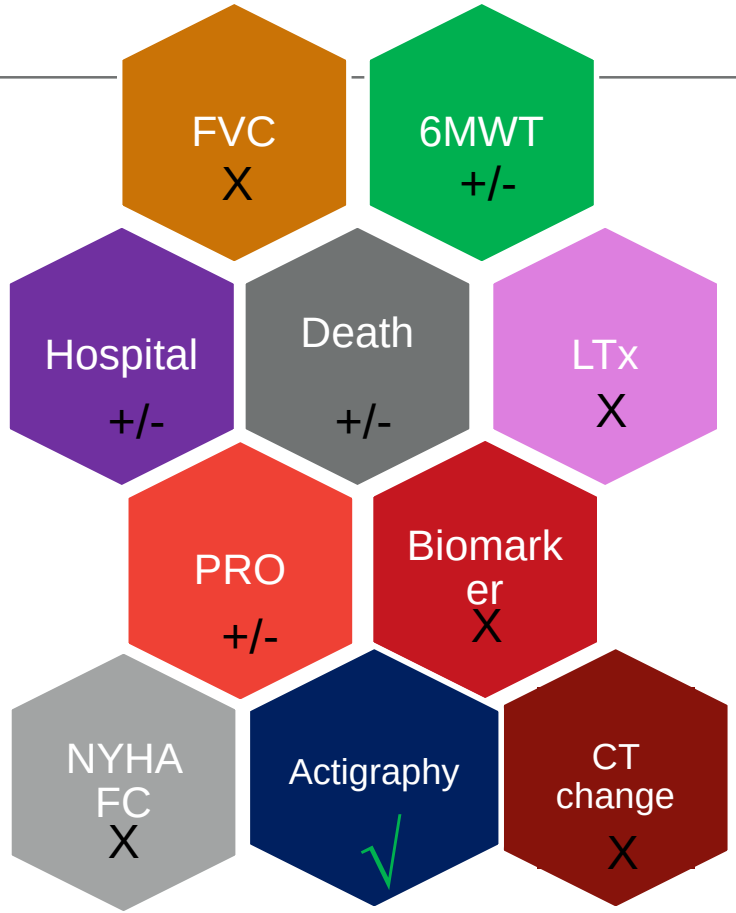
Voice of Patient: IPF Places Significant Burden on Daily Physical Activity

FDA: Provides Opportunities to Develop Better Outcome Measures in Future Trials

Impact on Daily Life	Most frequently mentioned – decrease of physical function Struggle to perform basic activities such as walking up stairs, showering, housework, and other everyday tasks Severe limits on mobility, difficulty with tasks requiring exertion
Symptoms of Reduced Physical Activity	Physical exertion triggers the most significant symptoms of coughing, shortness of breath and fatigue/malaise Difficulty with basic tasks results in inability to manage work and home life, isolation, impact on relationships and stigma
Treatment Desires	Slow down disease progression Mitigate the impact of the most significant symptoms and improve quality of life

US FDA, “Idiopathic Pulmonary Fibrosis - The Voice of the Patient Report”, March 2015

CLINICAL TRIAL ENDPOINTS IN ILD-PH: WHAT TO START WITH?



Actigraphy Provides a Direct Measure of Daily Physical Activity

6MWT
Surrogate for what patients can do

Daily Physical Activity

Actigraphy
- Direct and objective measurement of activity
- Continuous monitoring allows chronic evaluation
- Correlates to

Patient Reported Outcomes (PROs)
- Indirect assessment of activity
- Variability due to recall, bias, activity domains, etc.

Metabolic Cart & CPEX
- Direct measurement of METs/VO2
- Laboratory technique allowing only acute or short term assessment

The Value and Application of the 6-Minute-Walk Test in Idiopathic Pulmonary Fibrosis

A. Whitney Brown and Steven D. Nathan

Advanced Lung Disease and Transplant Program, Inova Heart and Vascular Institute, Inova Fairfax Hospital, Falls Church, Virginia

Beyond the 6-Minute-Walk Test: Is There a Role for Activity Monitors?

Interestingly, the 6MWT initially evolved from a 12-minute test, which was considered too exhausting for patients with respiratory disease. The test performance characteristics were not compromised with truncation to 6 minutes, and this has since been broadly accepted as a surrogate of patients' day-to-day activity ability (4). With the advent of activity monitors, technology has now enabled a platform to move beyond a surrogate and actually record patients' daily activity levels. The ability to monitor patients continuously and remotely is an exciting development that represents a new dimension for both clinical practice and research studies. Although there is a paucity of data on the use of activity monitors in IPF, there is a precedent for their use in chronic lung disease, where the majority of published experience is in the field of COPD (39). There are no large published studies in IPF;

Ann Am Thorac Soc Vol 15, No 1, pp 3–10, Jan 2018

Multiple Late Stage Trials Using Actigraphy as Primary Endpoint

Phase	Indication	Sponsor	Primary Endpoint	Secondary Endpoints
Phase IV	PAH (selexipeg vs placebo)	Actelion	Actigraphy	• WHO Functional Class • 6MWD • Borg Dyspnea • NT-ProBNP • PAH-Sympact Questionnaire
Phase IV	Heart Failure with Reduced Ejection Fraction (sacubitril/valsartan vs enalapril)	Novartis	Actigraphy	• Additional actigraphy parameters
Phase II/III	Pulmonary Fibrosis at Low or Intermediate/High Risk of Pulmonary Hypertension	Bellerophon	Actigraphy	• Additional actigraphy parameters • Oxygen Saturation
Phase III	Heart Failure with Reduced Ejection Fraction (sacubitril/valsartan vs enalapril)	Novartis	6MWD Actigraphy	• Additional 6MWD parameters • Additional actigraphy parameters
Phase III	COPD (portable oxygen concentrator vs standard of care)	Resmed & Inogen	Actigraphy	• St George Respiratory Questionnaire • Oxygen Usage • Hospital & Depression Scale
Phase II	Heart Failure with Preserved Ejection Fraction (HFpEF) (macitentan vs placebo)	Actelion	NT-ProBNP	• Actigraphy • Kansas City Cardiomyopathy Questionnaire • Time to Worsening

Continuous Physical Activity Monitoring (Actigraphy) Allows Objective Assessment of Daily Physical Activity

Continuous Monitoring of Physical Activity

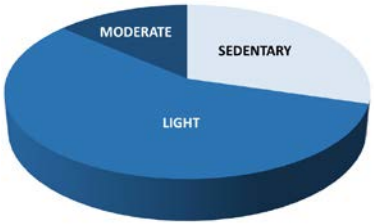
Subject wears actigraphy monitor on non-dominant arm

Monitor continuously measures movement in acceleration units

Movement is Categorized into Activity Intensity Levels

Activity Intensity	Example activities
Sedentary (<100 counts) (< 1.5 METs)	• Lying • Sitting • Computer work
Light (100 -1951 counts) (1.6 - 3.0 METs)	• Getting dressed • Bathing/showering • Light house cleaning
Moderate (1952-5724 counts) (3.1 - 6.0 METs)	• Walking • Ascending/descending stairs • Housework/Yardwork
Vigorous (>5724 counts) (> 6.0 METs)	• Slow/fast running • Intense sports

Provides Profile of Daily Activity



Subjects spend ~60 minutes per day in moderate physical activity

Subjects are unable to achieve vigorous activity levels

MVPA is the sum of moderate and vigorous activity

Top Line Results from iNO-PF Cohort 1 – Actigraphy and Oxygen Saturation

	iNO 30	Placebo	Placebo Corrected Change	
Moderate vigorous physical activity (MVPA) (minutes/day)	+8.1%	-26.1%	+34.2%	• Statistically significant improvement as compared to placebo (p=0.04) • Primary endpoint for pivotal Phase 3 cohort
Overall Activity (counts/min)	+0.0%	-11.9%	+11.9%	• Statistically significant improvement in as compared to placebo (p=0.05)
SpO2 Nadir	+0.3%	-1.4%	+1.7%	• Higher nadir for iNO=better saturation
Oxygen Desaturation (Percent Improvement)	+9.3%	-10.5%	+19.8%	• Reduced desaturation for iNO=better saturation

MVPA = moderate to vigorous physical activity

iNO-PF Phase 2/3 Study

…ambulatory NO: Primed for success?

- It works √
- It's given locally √
- It's well-tolerated √
  - e.g. no systemic hypotension
- It goes to the areas where it is "needed" √
- Targeted population broad √
- Cohort 1 results show great promise √
- Actigraphy is emerging as the "gold standard" for how patients truly function √

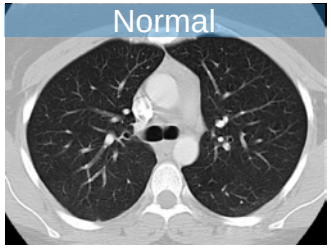
Bellerophon Therapeutics Clinical Update

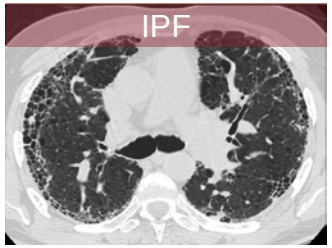
Hunter Gillies, M.D.
Chief Medical Officer
Bellerophon Therapeutics

Bellerophon THERAPEUTICS

PH Associated with ILD is Unmet Medical Need with Significantly Reduced Survival

Interstitial Lung Disease (ILD) is a broad category of diffuse lung diseases characterized by variable amounts of inflammation and fibrosis



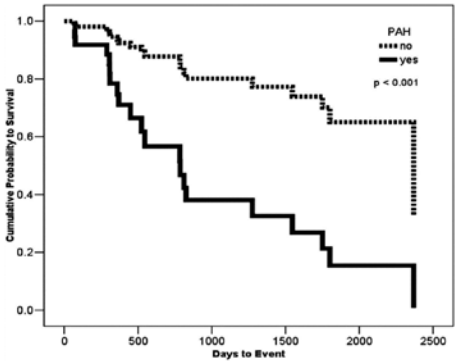


Idiopathic Pulmonary Fibrosis (IPF) is the largest and most serious of the many fibrotic subsets of ILDs

Patients with pulmonary fibrosis have thickening and scarring of the air sacs in the lungs, and often require supplemental oxygen to maintain adequate oxygen saturation

Prognosis and survival are significantly worse for patients with pulmonary hypertension

Pulmonary hypertension as predictor of survival in IPF



Approximately 40% of IPF patients exhibit symptoms of pulmonary hypertension at rest, including elevated pulmonary pressures

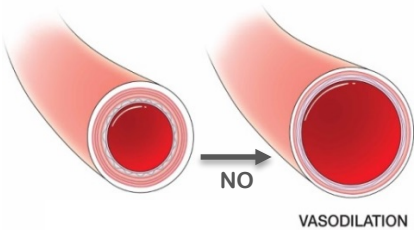
PH-IPF associated with a 3-fold increase in risk of death compared to IPF alone

No approved therapy for treating PH in these patients

INOpulse has the potential to provide targeted vasodilation while avoiding concerns of V/Q mismatch which have prevented current PAH systemic vasodilators to be approved for this unmet medical need

INOpulse Delivery System Overview

Portable Delivery System Allows Chronic iNO Therapy



Nitric Oxide is a well established vasodilator approved for acute treatment of persistent pulmonary hypertension in hospitals

Portable pulsatile iNO delivery system for chronic administration

INOpulse®

Novel drug-device combination therapy with dual mechanisms of action

Targeted pulmonary vasodilation

Ventilation/Perfusion (V/Q) matching

Hospital based continuous flow iNO delivery system for acute administration

INOmax®

Ikaria commercial platform sold to Mallinckrodt for $2.3B

Approved for use in persistent pulmonary hypertension in neonates

INOpulse Delivery System

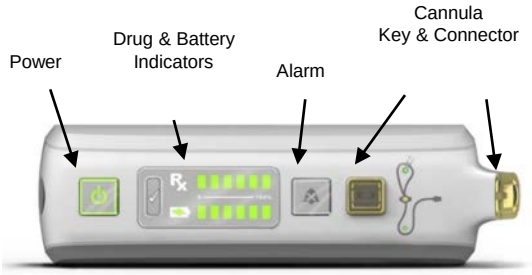
Lightweight, Portable and User Friendly

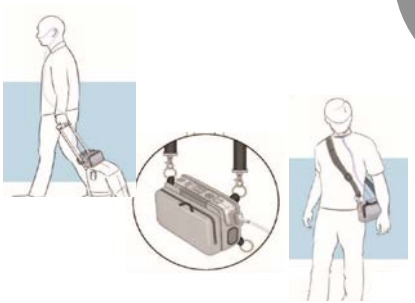
01 Swing engagement with drug cartridge

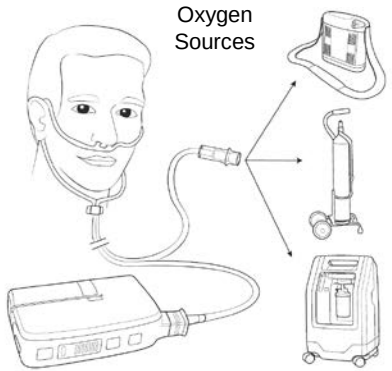
02 Intuitive and simple user interface

03 Tri-lumen cannula allows direct connection with oxygen

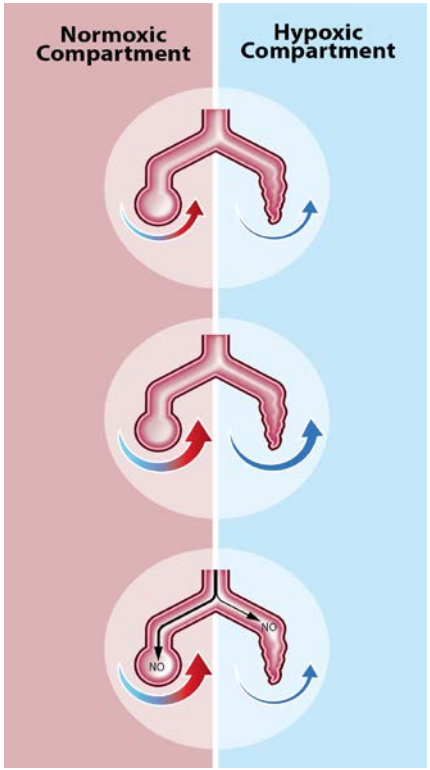
04 Lightweight portable design allows ease of transport







INOpulse Provides a Unique and Differentiating Mechanism of Action



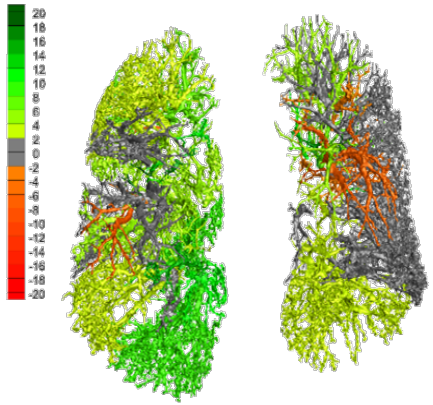
Baseline	Hypoxic pulmonary vasoconstriction prevents oxygen desaturation
Systemic Vasodilators	Systemic vasodilators can reverse hypoxic vasoconstriction leading to ventilation/perfusion (V/Q) mismatch and arterial O2 desaturation
INOpulse	Providing iNO early in the inspiratory phase allows for targeted vasodilation of only the well ventilated alveoli thereby preventing V/Q mismatch and O2 desaturation

Phase 2a Study PH-IPF

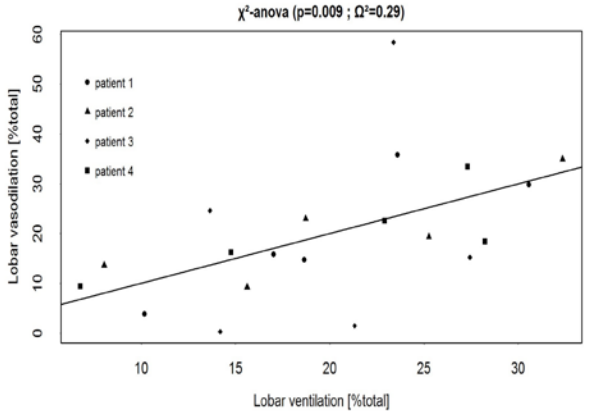
Acute Phase Data Showed Immediate Benefit of iNO on Vasodilation and Hemodynamics

- Significant correlation between ventilation and vasodilation, demonstrating selective vasodilation to better ventilated areas of the lung (p=0.009)
- Consistent and clinically meaningful reduction of 14% in systolic pulmonary arterial pressure (sPAP)
- Clinically meaningful improvement oxygen desaturation of 28.5% and SpO2 nadir of 5.5%

Targeted Vasodilation



Ventilation/Vasodilation Matching

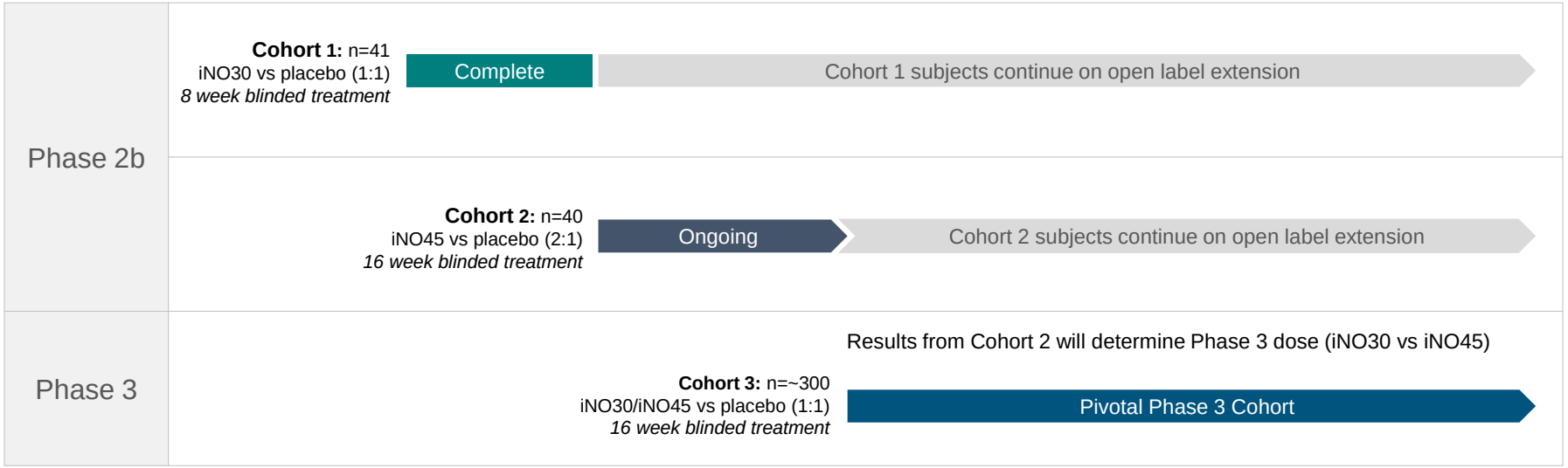


iNO-PF Phase 2/3 Study Design

Double-blind, placebo-controlled study in a broad population of pulmonary fibrotic interstitial lung diseases

Echocardiography used to stratify patients for low or intermediate/high risk of pulmonary hypertension

iNO-PF Phase 2/3 Study Design



FDA Agreement Allows Immediate Transition to Phase 3

FDA Agreements on Phase 2/3 Study Design

MVPA (moderate to vigorous physical activity) as measured by actigraphy is primary endpoint for Phase 3

Cohort 3 of ongoing iNO-PF study serves as the pivotal Phase 3 study for approval

Endpoints for Pivotal Phase 3 Cohort

Primary Endpoint: Change in moderate to vigorous physical activity (MVPA) measured via actigraphy from baseline to week 16

Secondary Endpoints:

- Change in overall activity (counts/minute) measured by via actigraphy
- Change in minutes of non-sedentary activity measured via actigraphy
- Change in SpO2 Nadir
- Change in oxygen desaturation

Continuous Physical Activity Monitoring (Actigraphy) Allows Objective Assessment of Daily Physical Activity

Continuous Monitoring of Physical Activity

Subject wears actigraphy monitor on non-dominant arm

Monitor continuously measures movement in acceleration units

Movement is Categorized into Activity Intensity Levels

Activity Intensity	Example activities
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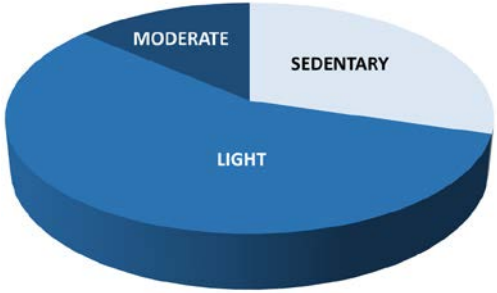
Provides Profile of Daily Activity



Subjects spend ~60 minutes per day in moderate physical activity

Subjects are unable to achieve vigorous activity levels

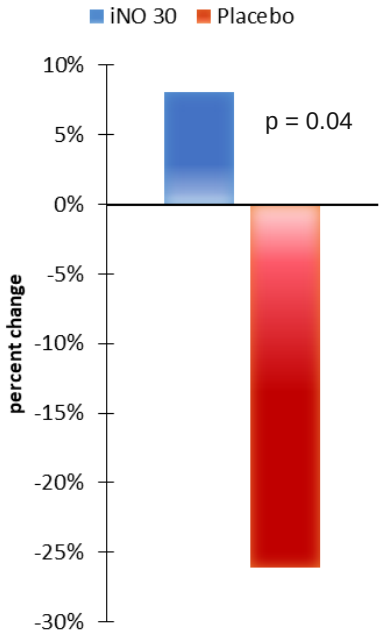
MVPA is the sum of moderate and vigorous activity

Cohort 1: Patient Demographics (N = 41)

	iNO 30 (n=23)	Placebo (n=18)	Total (n=41)
Males, n (%)	16 (70)	13 (72)	29 (71)
Age (mean, yrs)	68.5	65.8	67.3
IPF, n (%)	20 (87)	10 (56)	30 (73)
Intermediate to High Probability of PH, n (%)	15 (65)	14 (78)	29 (71)
DLCO (mean, % predicted of normal)	30.7	30.4	30.5
Baseline FVC (mean, % predicted of normal)	56.3	59.9	57.9

Cohort 1: Clinically and Statistically Significant Improvement in MVPA (moderate to vigorous physical activity)

MINUTES/DAY IN MVPA

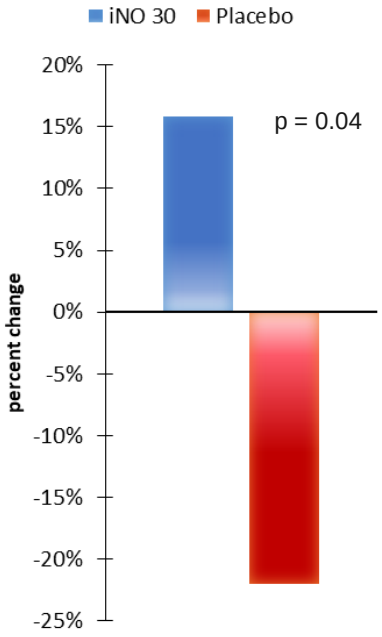


RESPONDER ANALYSIS

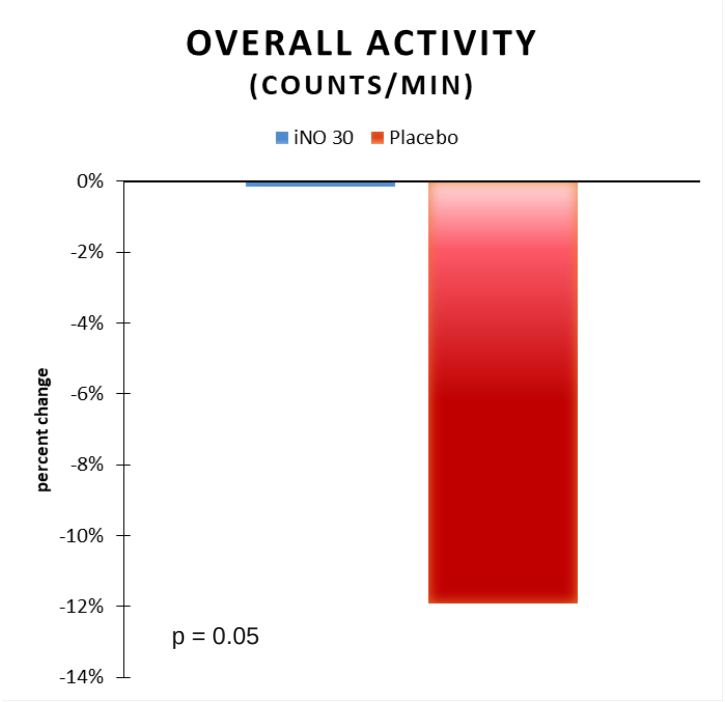
Change from Baseline	iNO 30	Placebo	
> +15%	**23%**	**0%**	**Clinically Significant Improvers**
0 to +15%	23%	14%	
0 to -15%	15%	14%	
< -15%	**39%**	**71%**	**Clinically Significant Decliners**

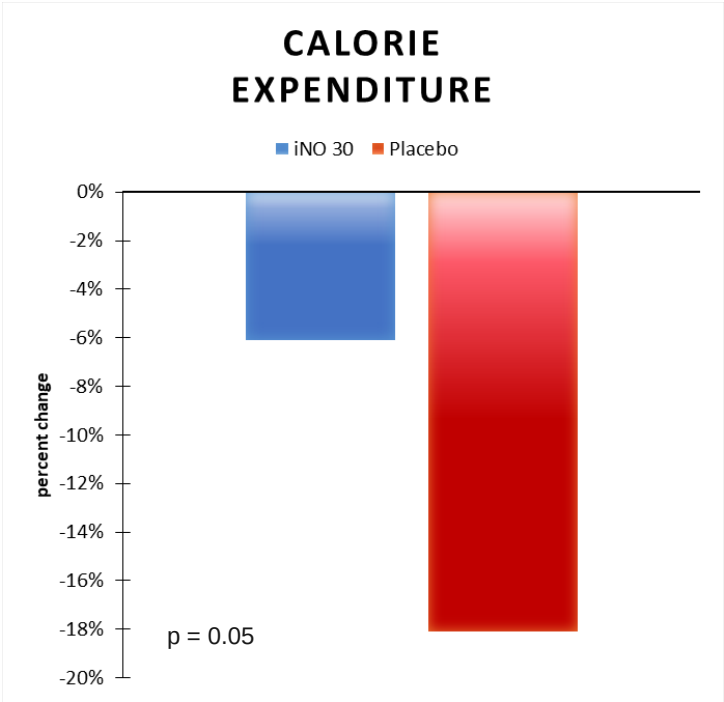
Clinically significant change is considered >15% from baseline

PORTION OF TIME IN MVPA



Cohort 1: Clinically and Statistically Significant Improvement Observed in Additional Physical Activity Parameters

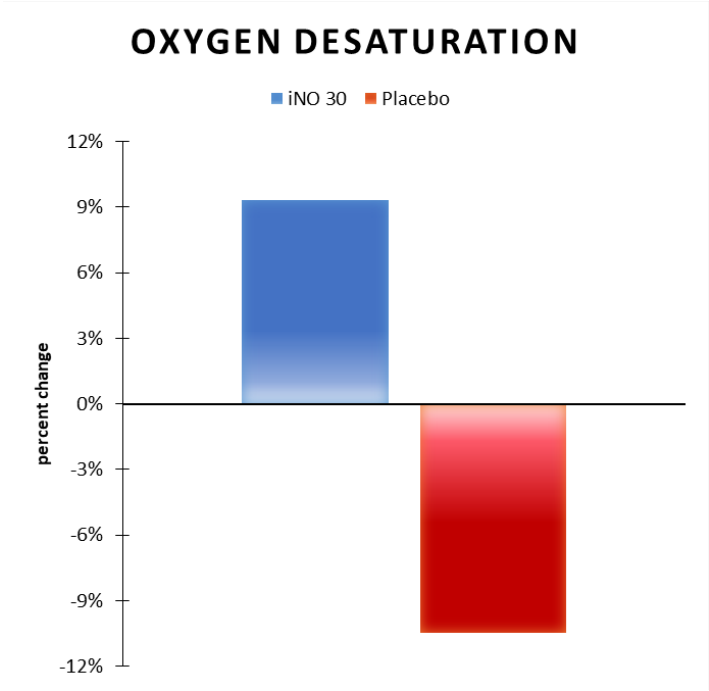


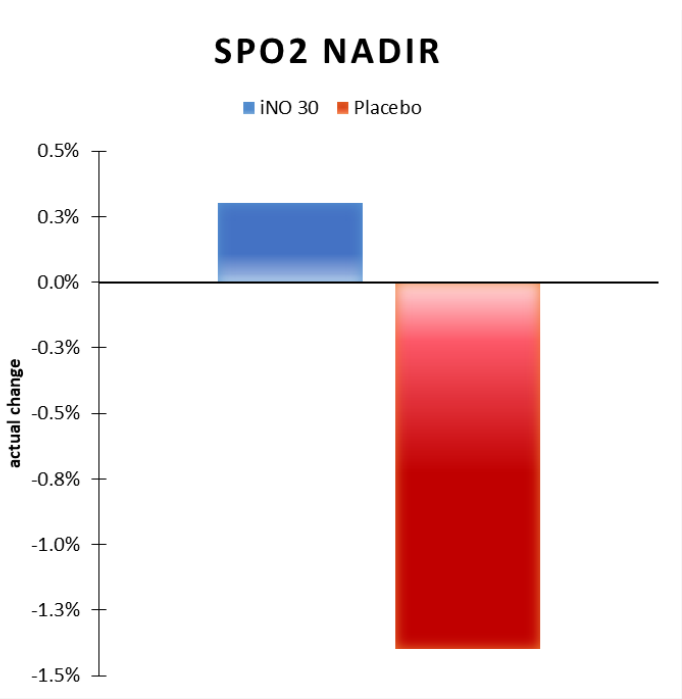


Overall activity is measured in counts, a magnitude of a subject's daily movement as measured via tri-axial acceleration

Cohort 1: Increased Oxygen Saturation Supports Improvements in Activity

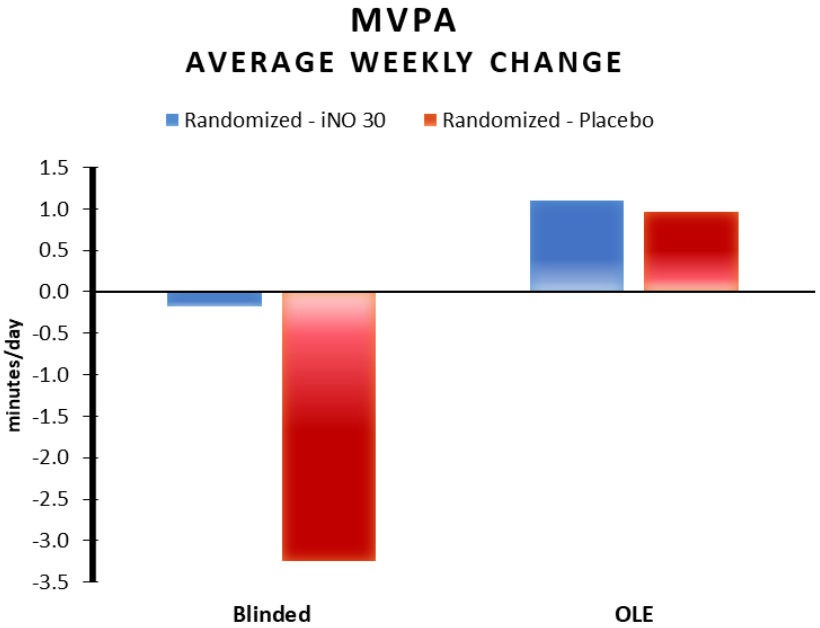
Improvements in Oxygen Saturation Consistent with INOpulse's Targeted Delivery to Well Ventilated Alveoli

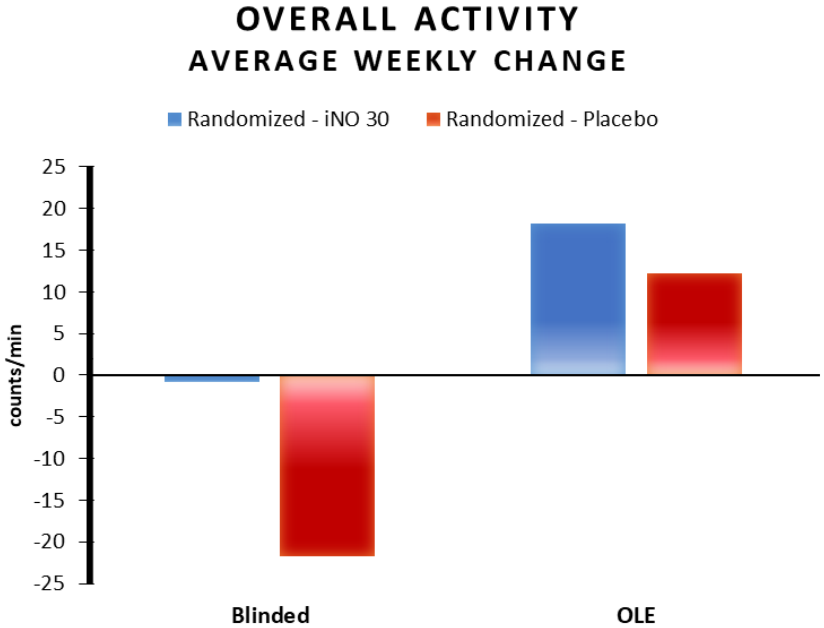




Cohort 1: Continued Benefit for Subjects on Open Label Extension (OLE)

Subjects Transitioning from Placebo to Active saw Trend Reversal from Deterioration to Improvement in both MVPA and Overall Activity





MVPA = moderate to vigorous physical activity;

Overall activity is measured in counts, a magnitude of a subject's daily movement as measured via tri-axial acceleration

Cohort 1: Safety Summary

- Pulsed Inhaled Nitric Oxide was well tolerated at iNO 30 dose in Cohort 1
  - Incidence of AEs and SAEs was low in both active and placebo groups and was balanced across both groups
  - All SAEs were reported as unrelated to the Study drug

- There were no unexpected AEs or SUSARs reported

	iNO 30 N=23	Placebo N=18
Adverse Events	15 (65.2%)	13 (72.2%)
Serious Adverse Events	2 (8.7%)	2 (11.1%)
Deaths	1 (4.3%)	0
Discontinuations	2 (8.7%)	2 (11.1%)

SUSAR = Serious Unexpected Suspected Adverse Reaction

Summary of iNO-PF Cohort 1 Clinical Results

- Statistically significant placebo corrected improvement of 34% in MVPA
- Additional activity parameters (overall activity, percent of time in MVPA and calories) also show consistent and statistically significant benefit
- INOpulse targeted delivery improves oxygen saturation during exercise
- Consistent improvement in MVPA and Overall Activity for subjects on open label extension
- Pulsed inhaled NO was safe and well tolerated

Planned Next Steps in PH-ILD

Cohort 2 iNO45 vs placebo	• Planned enrollment increased to 40 subjects • Over 50% recruitment achieved • Study completion expected in 2H2019
Cohort 3 Pivotal Phase 3 Study iNO30/iNO45 vs placebo	• Results from Cohort 2 will determine optimal dose (iNO30 or iNO45) • Planned enrollment of approximately 300 subjects (150 per arm) • Initiate study after readout of Cohort 2 in 1Q2020 • Primary endpoint is change in MVPA (moderate to vigorous physical activity) as measured via actigraphy • Estimated enrollment period 18-24 months

PH-ILD Steering Committee Members

Member	Affiliation
Steven Nathan MD Steering Committee Chair	Professor of Medicine at Virginia Commonwealth University Inova Campus, Director of the Advanced Lung Disease Program and Director of the Lung Transplant Program at Inova Fairfax Hospital.
Kevin Flaherty MD	Professor, Department of Internal Medicine, University of Michigan, Associate Director, T32 Multidisciplinary Training Program in Lung Diseases, Chair of Pulmonary Fibrosis Foundation Clinical Care Network Steering Committee
Marilyn K Glassberg Ceste MD	Professor, University of Miami Health System and Director, Interstitial Lung and Pulmonary Diseases at Interdisciplinary Stem Cell Institute, University of Miami School of Medicine
Lisa Lancaster MD	Associate Professor, Division of Allergy, Pulmonary and Critical Care Medicine Vanderbilt University Medical Center, Nashville TN and Clinical Director Interstitial Lung Disease and Adult Cystic Fibrosis Programs
Ganesh Raghu MD	Professor of Medicine in the Division of Pulmonary and Critical Care Medicine University of Washington, Director of the Interstitial Lung Disease/Sarcoid/Pulmonary Fibrosis Program, Medical Director of the Lung Transplant Program Pulmonary & Critical Care Medicine
Jeffrey Swigris MD	Associate Professor, Department of Medicine, National Jewish, Denver Colorado, Division of Pulmonary, Critical Care and Sleep Medicine

PH-Sarcoidosis and PH-COPD Program Status

Pulmonary Hypertension associated with Sarcoidosis

Inhaled nitric oxide has been shown to improve hemodynamics and exercise capacity

Phase 2 study is ongoing to verify INOpulse hemodynamic effect and identify optimal dose

- Acute dose escalation study with right heart catheterization
- Assess safety and hemodynamic parameters

Study results expected in 2H2019

Pulmonary Hypertension associated with Chronic Obstructive Pulmonary Disease (COPD)

Multiple Phase 2 studies have established targeted delivery to well ventilated alveoli and benefit on exercise capacity and hemodynamics

Phase 2b study design reviewed and finalized with FDA

- Multiple endpoints including activity monitoring and oxygen saturation
- Study will assess multiple doses to allow finalization of Phase 3 program

Study to be initiated in 2020

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