A Randomized, double-blind, placebo-controlled study to assess the safety and efficacy of pulsed, inhaled nitric oxide (iNO) at a dose of 30 mcg/kg-IBW/hr (iNO 30) in subjects at risk of Pulmonary Hypertension associated with Pulmonary Fibrosis (PH-PF) on Long Term Oxygen Therapy

Study sponsored by Bellerophon Therapeutics

American Thoracic Society Annual Meeting – May 20, 2019

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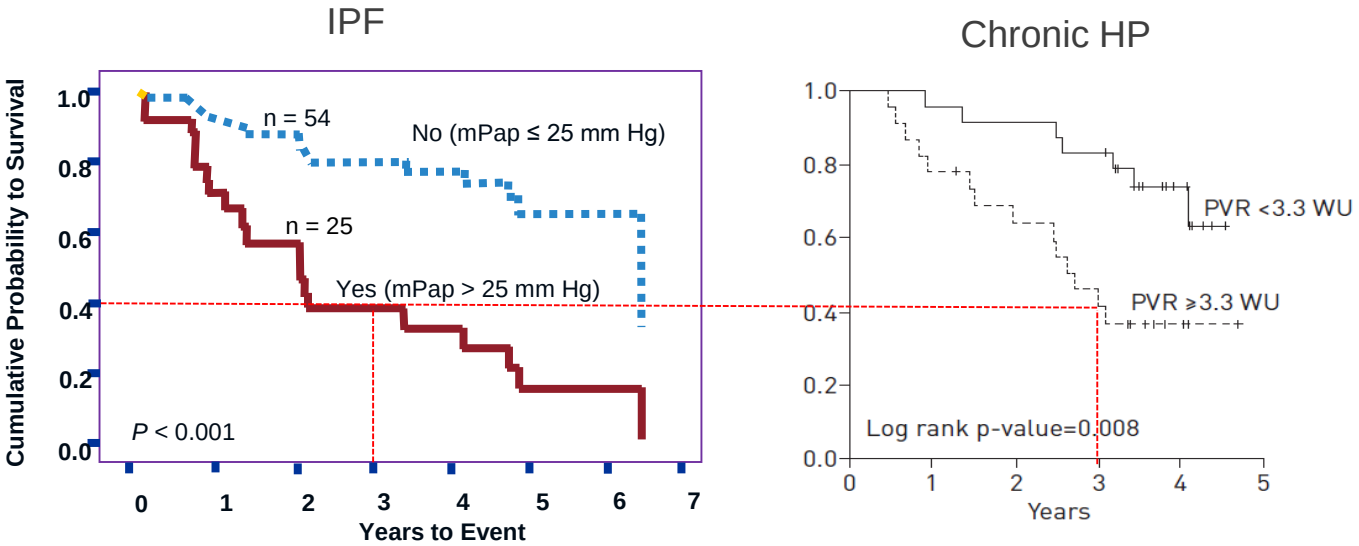
Presence of PH Associated with Worse Outcomes in ILD

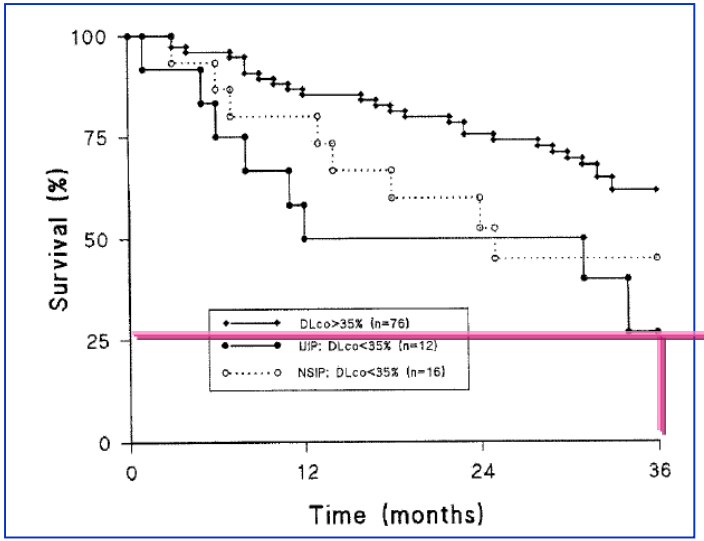


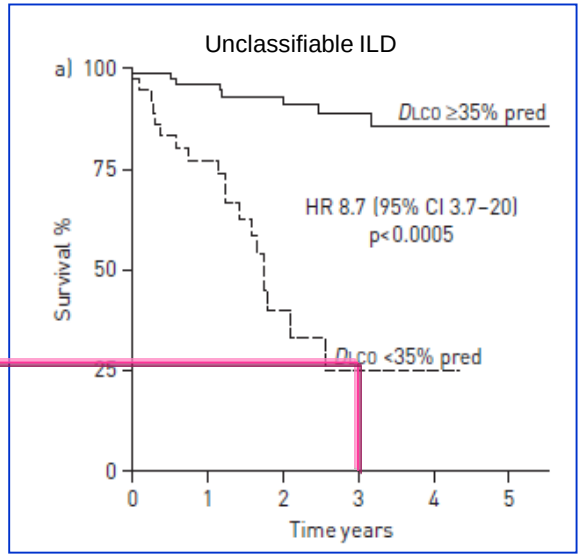
Chest. 2006;129:746-752.

Eur Respir J 2018; 51: 1800430.

Chronic HP = Chronic Hypersensitivity Pneumonia

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.

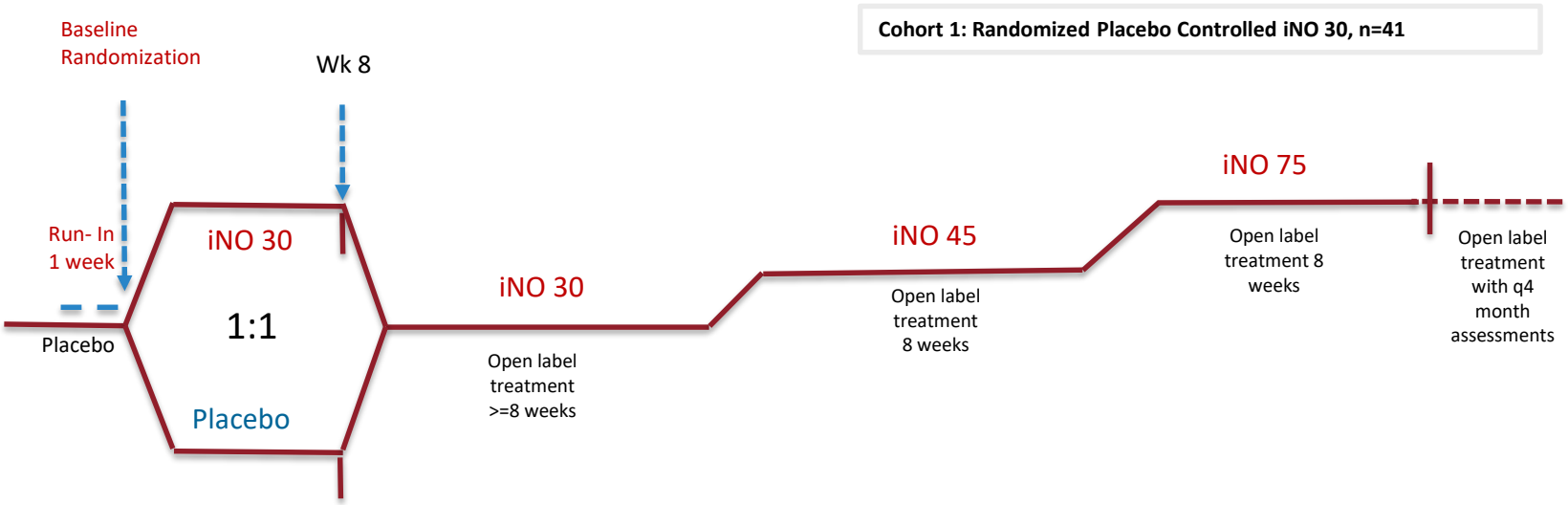
Study Objective

Phase 2b, randomized, double-blind, placebo-controlled dose escalation study to assess the safety and efficacy of pulsed iNO versus placebo in patients at risk of pulmonary hypertension (PH) associated with pulmonary fibrosis (PF) on long term oxygen therapy (LTOT).

<u>Seamless Phase 2b/3 Program:</u>

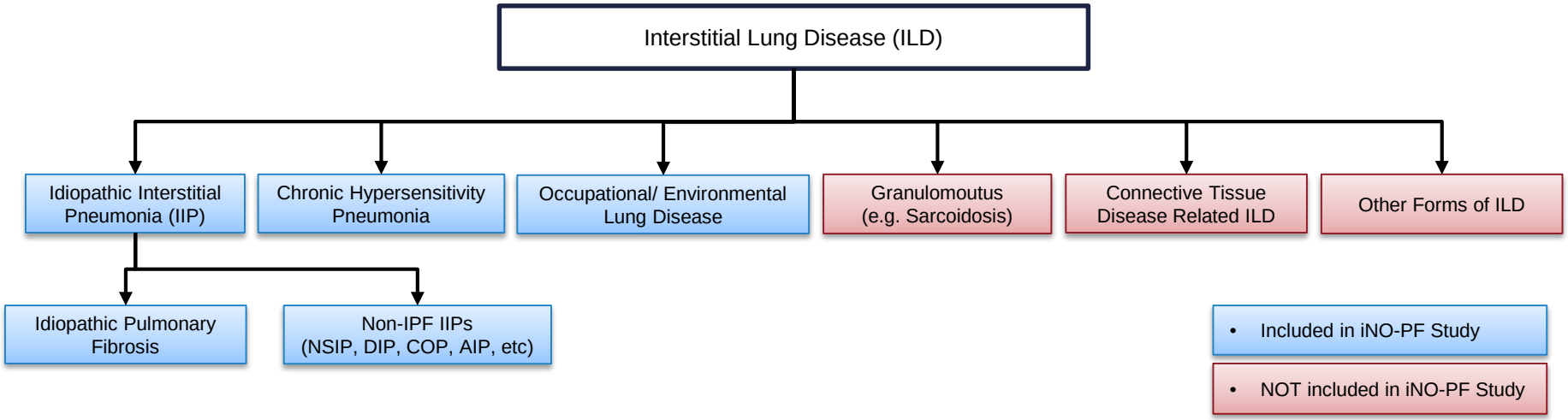
- Cohort 1: iNO30 vs placebo for 8 weeks
  - Cohort 2: iNO45 vs placebo for 16 weeks
    - Phase 3 - Cohort 3: iNO30/45 vs placebo for 16 weeks

iNO-PF Cohort 1 Study Design



iNO-PF Phase 2b Study Design

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



Major Inclusion Criteria

- Age 18 and 85 years
- At least 50% of subjects with intermediate or high probability PH on echo (2015 ESC/ERS Guidelines)
- O_2 by nasal cannula for at least 4 weeks
- 6MWD ≥ 100 meters and ≤ 450 meters
- WHO Functional Class II-IV
- FVC≥ 40% predicted within last 6 months
- Willingness and demonstrated ability to use INOpulse delivery device for ≥ 12 hours per day
- Completed at least 1 week of activity monitoring at time of the Baseline/Randomization visit.

Major Exclusion Criteria

- Demonstrate symptomatic rebound, occurring within 1 hour of acute iNO during rebound testing
- Evidence of clinically significant CPFE

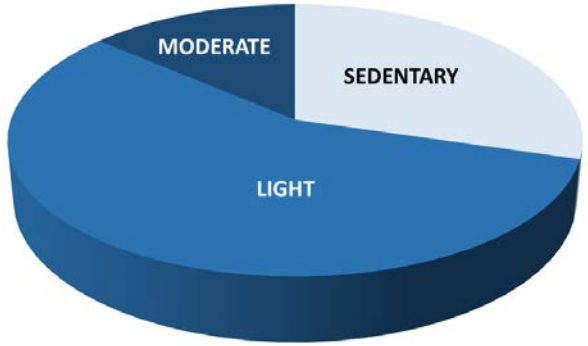
Cohort 1 Exploratory Efficacy Endpoints

Multiple efficacy parameters including:

- Change in 6-minute walk test parameters
- Difference in activity as measured by activity monitoring from baseline
- Percentage of patients with ≥15% decrease in activity monitoring from baseline
- Change in NT-ProBNP
- Change in SpO2 Nadir
- Change in Oxygen Desaturation
- Change in Distance Saturation Product (Composite of 6MWD & SpO2 Nadir)

Continuous Activity Monitoring Allows Objective Assessment of Daily Physical Activity

Wrist Worn Actigraph
Subject wears actigraphy monitor on non-dominant arm
Monitor continuously measures movement in acceleration units
Activity categorized by intensity (sedentary, light, moderate, vigorous)



Assessment of Daily Activity Levels	
Activity Intensity	**Example activities**
Sedentary	Lying, Standing, Computer work
Light	Washing dishes, Washing windows, Vacuuming
Moderate	Walking, Ascending/descending stairs, Lawn mowing
Vigorous	Slow/fast running, Intense sport

iNO-PF 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

Results from iNO-PF Cohort 1 - Actigraphy

	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
Proportion of awake time in MVPA	+15.8%	-22.0%	+37.8%	• Statistically significant improvement in as compared to placebo (p=0.04)
Overall Activity (counts/min)	+0.0%	-11.9%	+11.9%	• Statistically significant improvement in as compared to placebo (p=0.05)
Calories	-6.1%	-18.1%	+12.0%	• Statistically significant improvement in as compared to placebo (p=0.05)

MVPA = moderate to vigorous physical activity

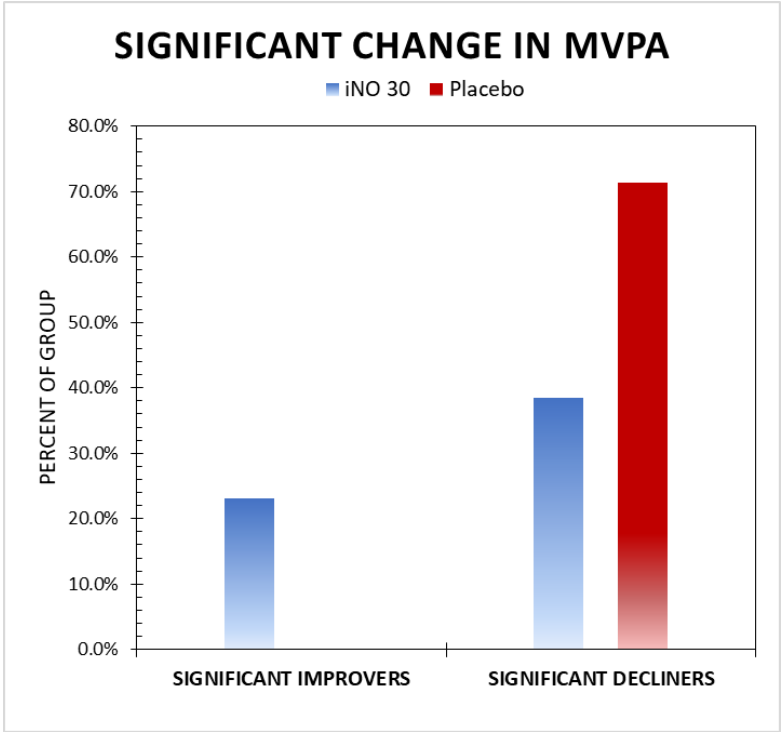
Supporting Results from iNO-PF Cohort 1

	iNO 30	Placebo	Placebo Corrected Change	
Oxygen Desaturation (Percent Improvement)	+9.3%	-10.5%	+19.8%	• Reduced desaturation for iNO=better saturation
SpO2 Nadir	+0.3%	-1.4%	+1.7%	• Higher nadir for iNO=better saturation
NT-ProBNP (% change)	+15.6%	+42.9%	-27.3%	• Peptide marker indicator of cardiac failure • Larger increase in placebo indicative of disease worsening
6MWD	+7.2 m	+0.5 m	+6.7 m	
Distance Saturation Product (DSP)	+8.5 m%	-2.0 m%	+10.5 m%	• Composite of 6MWD and SpO2 Nadir

iNO30 Maintains MVPA Compared to Consistent Decline in Placebo Group

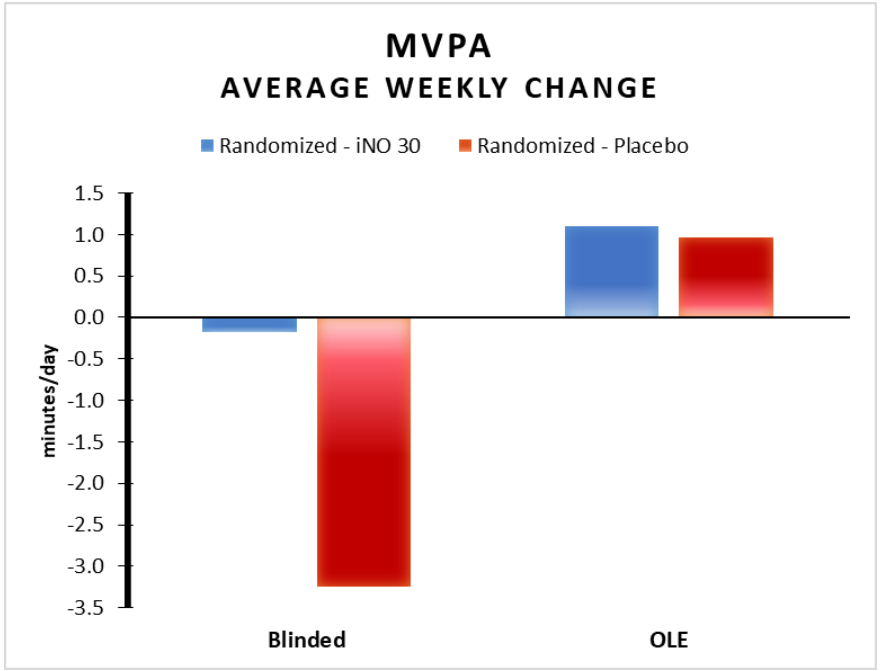
Change in MVPA of 15%+ is Considered Significant Change

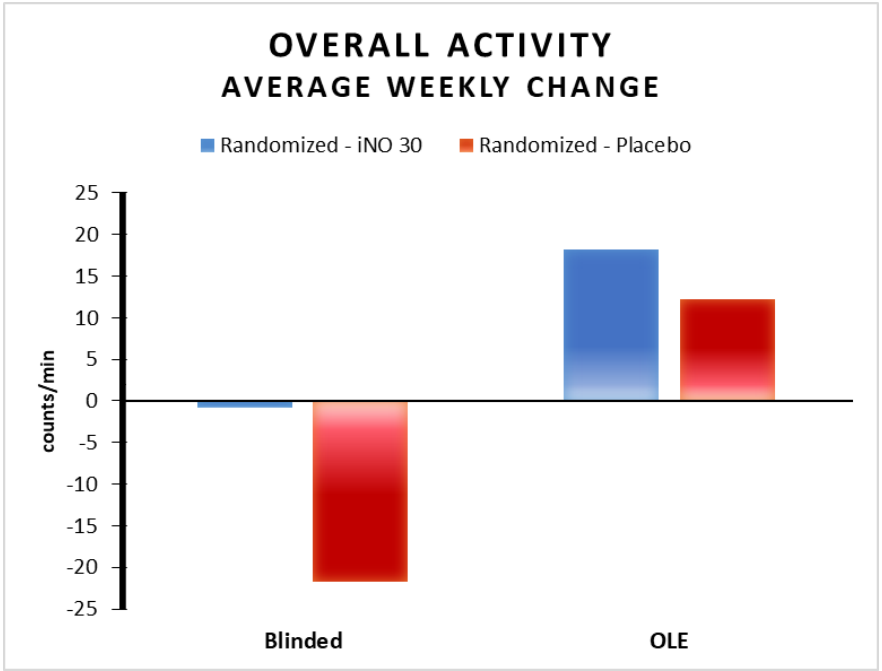
Change from Baseline	iNO 30	Placebo	
> +15%	**23%**	**0%**	**Significant Improvers**
0 to +15%	23%	14%	
0 to -15%	15%	14%	
< -15%	**39%**	**71%**	**Significant Decliners**



MVPA = moderate to vigorous physical activity

Consistent Improvement for Subjects on Open Label Treatment





Assessment based on 16 subjects with evaluable blinded and open label actigraphy data

MVPA = moderate to vigorous physical activity

OLE = Open label Extension

Cohort 1 Safety Summary (Part 1)

- 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

- Safety data supported dose escalation into the iNO 45 Cohort 2

	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

iNO-PF Modified into Seamless Phase 2/3 Based on Cohort 1 Results

FDA agreement on modification of Cohort 3 into pivotal Phase 3 study with MVPA (moderate to vigorous physical activity) as primary endpoint

- Cohort 1: Statistically significant improvement in MVPA and supported by improvements in activity and other cardiopulmonary endpoints
- Cohort 2: Ongoing to assess higher dose (iNO 45) and longer duration of treatment (16 weeks)
- Cohort 3: Pivotal Phase 3 cohort using MVPA as primary endpoint

iNO-PF Phase 2/3 Study Design