Open Label Dose Escalation Data from the Randomized, Double-Blind, Placebo-Controlled Study to Assess the Safety and Efficacy of Pulsed, Inhaled Nitric Oxide in Subjects at Risk of Pulmonary Hypertension Associated with Pulmonary Fibrosis (PH-PF)

Study sponsored by Bellerophon Therapeutics

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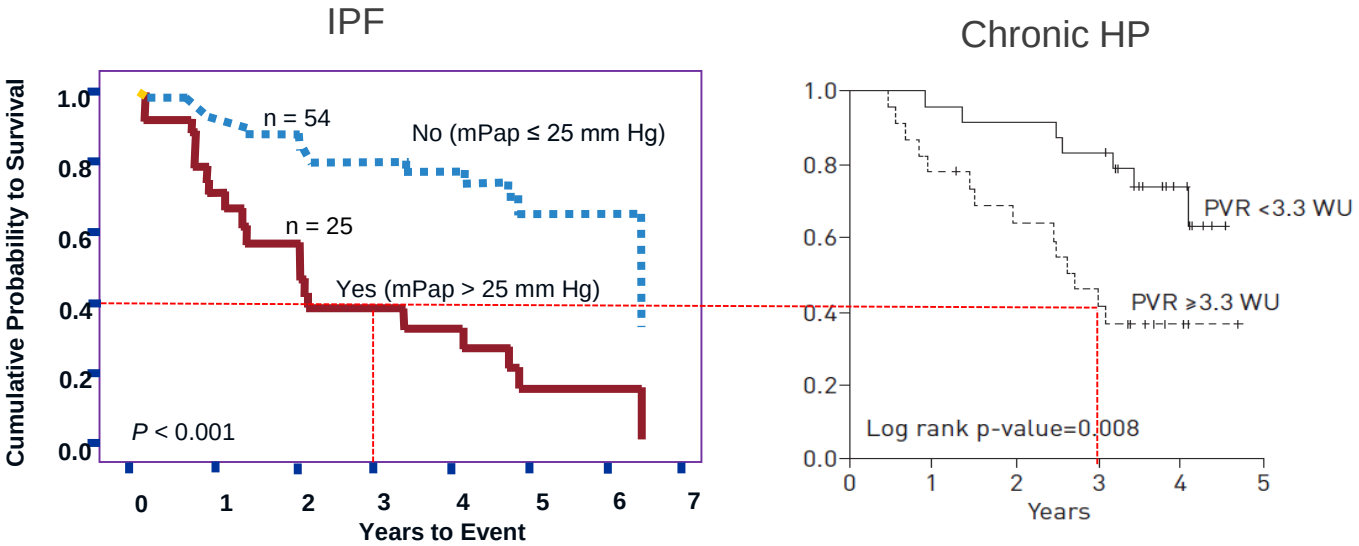
Steven D. Nathan, M.D., F.C.C.P.
Advanced Lung Disease and Lung Transplant Program, Inova Fairfax Hospital

K. Flaherty, M. K. Glassberg, G. Raghu, J. Swigris, R. Alvarez, N. Ettinger, J. Loyd, P. Fernandes, H. Gillies, P. Shah, L. Lancaster

Presence of PH Associated with Worse Outcomes in ILD



Chest. 2006;129:746-752.

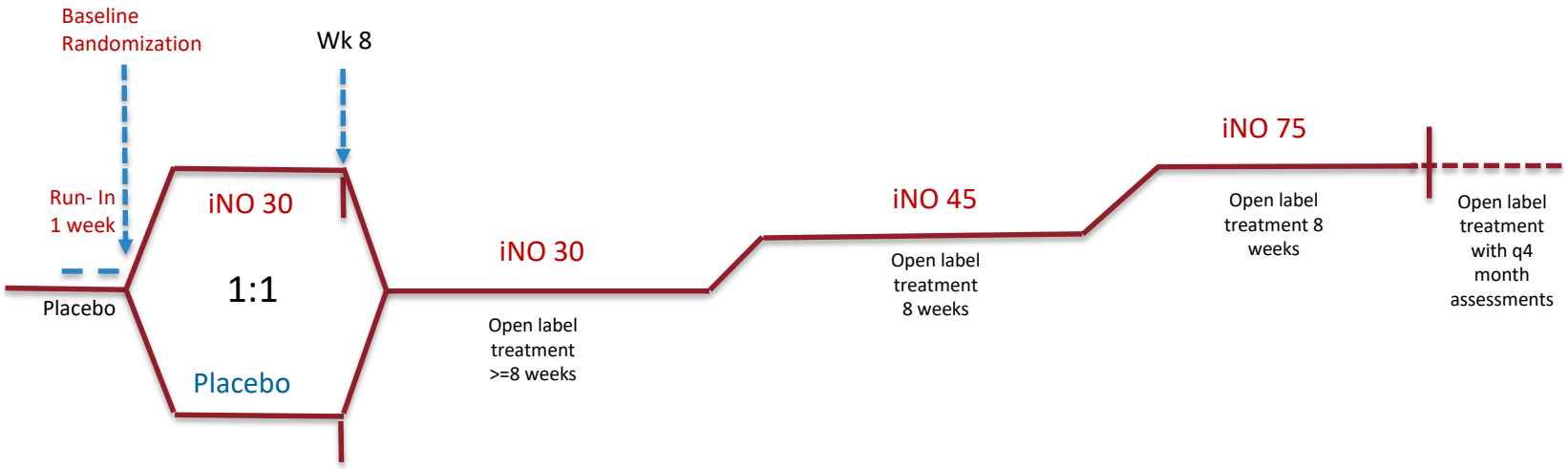
Eur Respir J 2018; 51: 1800430.

Chronic HP = Chronic Hypersensitivity Pneumonia

iNO-PF Study Design

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)

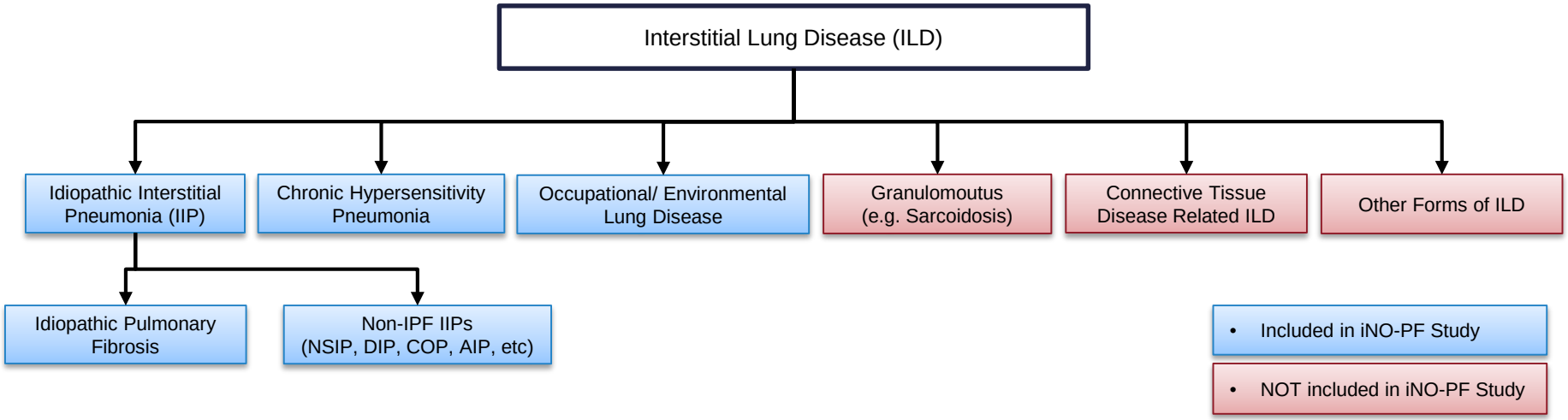
<u>Cohort 1</u>: Randomized Placebo Controlled iNO 30, n=41



- Top-Line Results on blinded treatment and initial open label results presented at American Thoracic Society 2019 Annual Meeting

iNO-PF Study Patient Population

Broad population of pulmonary fibrotic interstitial lung diseases



Eligibility Criteria

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

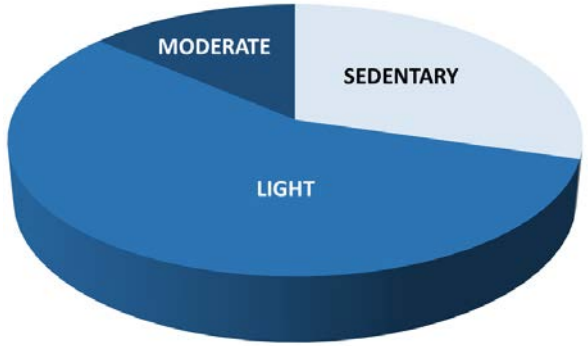
Cohort 1 Exploratory Efficacy Endpoints

Multiple efficacy parameters including:

- Difference in activity as measured by activity monitoring from baseline
- Percentage of patients with ≥15% decrease in physical activity from baseline
- Change in 6-minute walk test parameters
- 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)

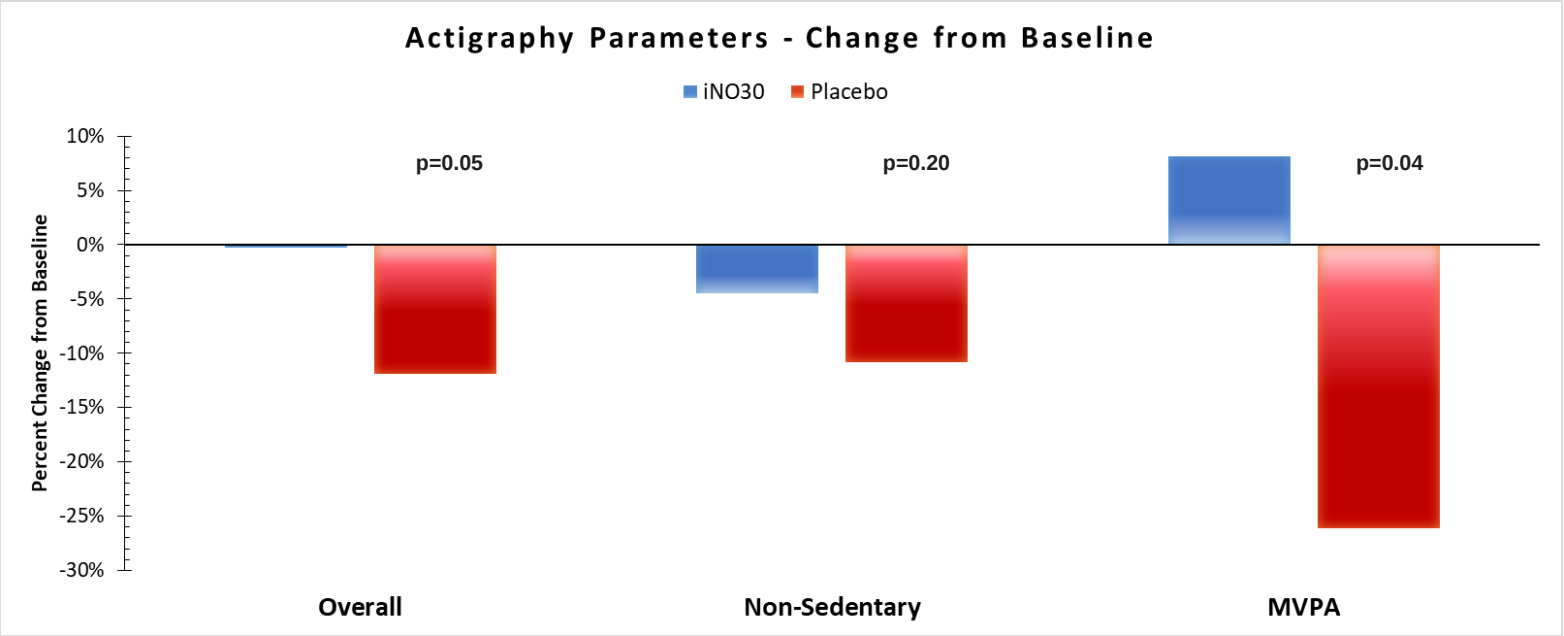


Assessment of Daily Activity Levels	
Activity Intensity	**Example activities**
Sedentary	Lying, Standing, Computer work
Light	Washing dishes, Washing windows, Vacuuming
Moderate	Walking, Ascending/descending stairs, Lawn mowing
Vigorous	Slow/fast running, Intense sport

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
Baseline 6MWD (meters)	293.8	271.4	284.0

Percent Change from Baseline After 8 Weeks of Blinded Treatment



- MVPA – moderate to vigorous physical activity
- Percent change is calculated as absolute change/baseline, e.g. Δ MVPA (minutes)/Baseline MVPA (minutes).
- Statistical analysis was conducted for active vs. placebo via student t.test at week 8 on available data.

Responder Analysis (± 15%): Clinically Important Improvement on iNO compared to Placebo

	Overall		Non-Sedentary		MVPA		
Change from Baseline	iNO 30	Placebo	iNO30	Placebo	iNO30	Placebo	
> 15% improvement	**15.4%**	**0.0%**	**7.7%**	**0.0%**	**23.1%**	**0.0%**	**Clinically Significant Improvers**
0 to 15% improvement	46.2%	14.3%	30.8%	14.3%	23.1%	14.3%	
0 to 15% decline	23.1%	64.3%	38.5%	42.9%	15.4%	14.3%	
< 15% decline	**15.4%**	**21.1%**	**23.1%**	**42.9%**	**38.5%**	**71.4%**	**Clinically Significant Decliners**

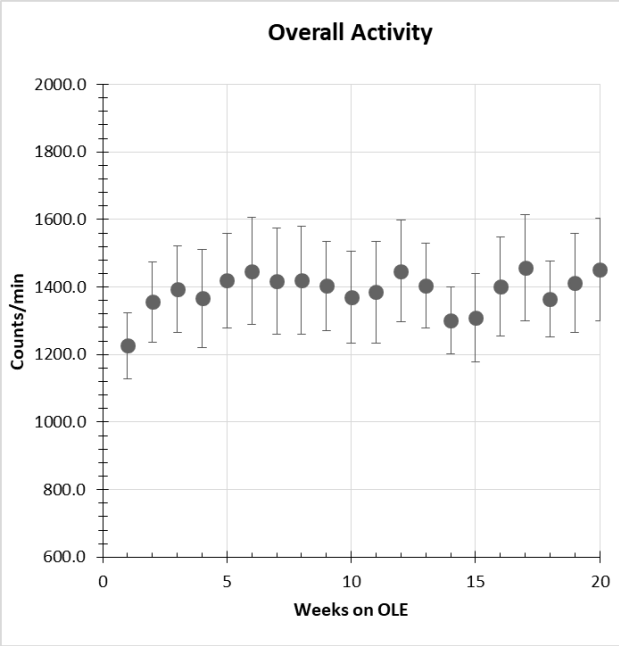
- MVPA – moderate to vigorous physical activity

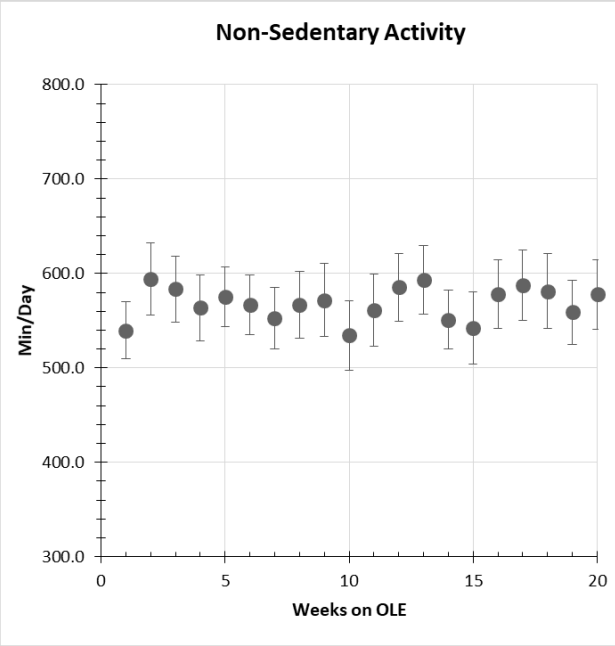
Improvement in Oxygen Saturation and DSP on iNO

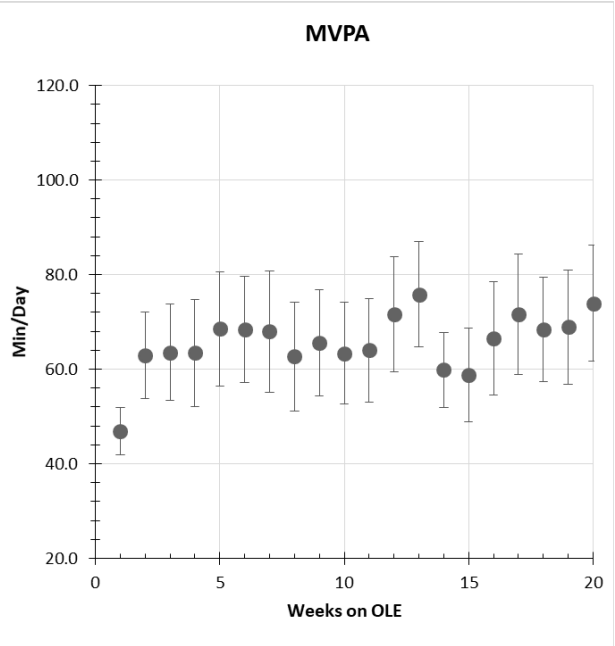
	iNO 30 (change from baseline)	Placebo (change from baseline)	Difference
Relative Oxygen Desaturation	-9.3% (8.0%)	10.5% (12.6%)	19.8% (14.2%)
SpO2 Nadir	0.3% (0.7%)	-1.4% (1.6%)	1.7% (1.5%)
6MWD (meter)	7.2 (11.7)	0.5 (6.7)	6.7 (18.8)
Distance Saturation Product (meter %)	8.5 (11.2)	-2.0 (16.4)	10.5 (19.1)

- Relative oxygen desaturation is calculated as: (Desaturation at end of study – Desaturation at baseline) ÷ Desaturation at baseline; a negative number indicates a reduction in desaturation as compared to baseline
- Distance saturation product is calculated as: 6MWD × SpO2 Nadir
- Standard errors for each parameter are provided in the parentheses.

Open Label Extension (OLE) Data Shows Long Term Maintenance of Activity Levels



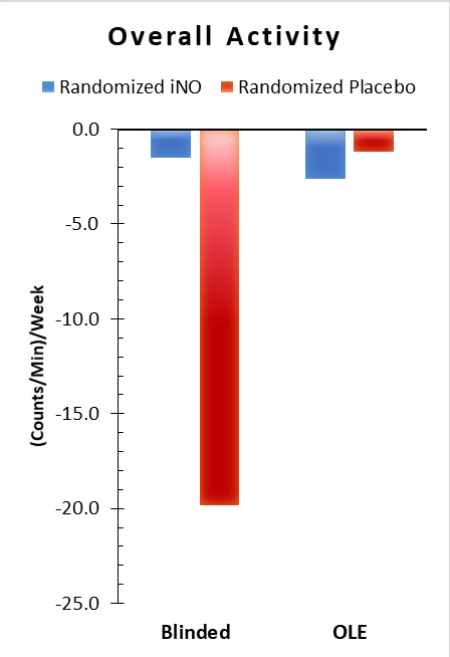


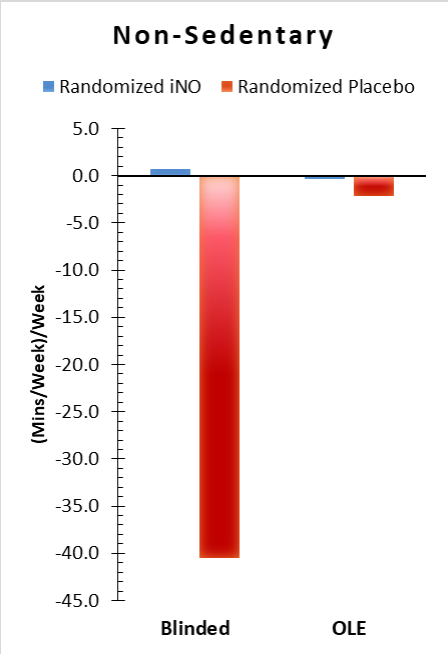


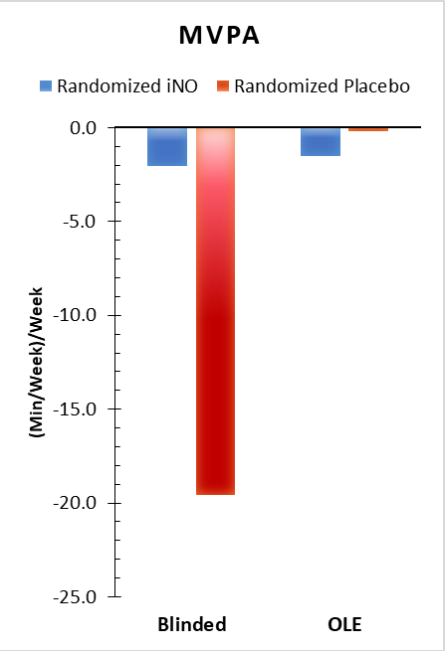
- Each data point represents the average for the week; error bars are standard error
- Analysis based on subjects with available OLE data (n=18)
- MVPA = moderate to vigorous physical activity

Subjects Randomized to Placebo Transition from Decline to Maintenance on OLE

Subjects randomized to iNO30 maintained activity levels when transitioning to OLE







- Assessment is based on 18 subjects with evaluable blinded and open label actigraphy data
- MVPA = moderate to vigorous physical activity
- Change is based on linear regression of available data during blinded treatment and open label treatment (average 27 weeks of OLE)

Cohort 1 Safety Summary (Part 1)

	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%)

- Adverse Events balanced across the treatment groups
- Low rate of discontinuation
- No rebound effect associated with the use of iNO
- No SUSARs

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 of overall activity and non-sedentary activity also show placebo corrected improvement
- Responder analysis shows maintenance in multiple activity parameters on iNO30 compared to consistent decline on placebo
- Open label extension data shows long-term maintenance in multiple activity parameters
- Subjects randomized to placebo transition from decline to maintenance during open label extension
- Pulsed iNO 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