# Actigraphy as a clinically meaningful endpoint to detect change after treatment with iNO (30 mcg/kg-IBW/hr) in patients at risk of Pulmonary Hypertension associated with Pulmonary Fibrosis

**S.D. Nathan[1], K. Flaherty[2], M. K. Glassberg[3], G. Raghu[4], J. Swigris[5], R. Alvarez[3], N. Ettinger[6], J. Loyd[7], P. Fernandes[8], H. Gillies[8], P. Shah[8], L. Lancaster[7]**

1. Virginia Commonwealth University and Inova Fairfax Hospital, 2. University of Michigan, 3. University of Miami, 4. University of Washington Medical Center, 5. Department of Medicine, National Jewish, Denver Colorado, 6. The Lung Research Center – Missouri, 7. Vanderbilt University Medical Center, 8. Bellerophon Therapeutics

**Background:**

Pulmonary fibrosis (PF) is made up of a wide variety of fibrotic lung diseases, the largest of which is IPF (Idiopathic Pulmonary Fibrosis). Pulmonary Hypertension associated with Pulmonary Fibrosis (PH-PF) is associated with a high rate of mortality and morbidity and poorer health outcomes. PH-PF often manifests in hypoxemia, impaired functional status and reduced physical activity.[1] There are currently no approved therapies to treat PH-PF and no established regulatory endpoints.

**Aim:**

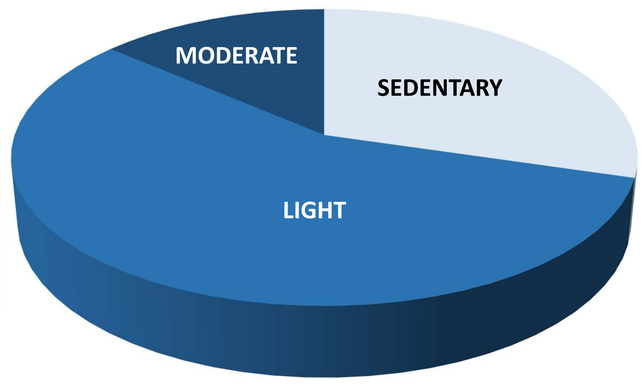
- To determine if wearable activity monitoring (actigraphy) can provide clinically meaningful data sensitive to functional change after treatment with iNO
- To evaluate if actigraphy could serve as a regulatory endpoint for future pivotal studies

**Methods:**

iNO-PF is a double-blind, placebo-controlled Phase 2b study assessing the safety and efficacy of pulsed inhaled nitric oxide (iNO), delivered by the INOpulse® delivery system, at a dose of 30 mcg/kg-IBW/hr (iNO 30) in subjects at risk of PH-PF. Subjects were randomized to receive iNO 30 (23 subjects) or placebo (18 subjects) for 8 weeks of blinded treatment. A wrist-worn medical grade activity monitor was used to assess changes in daily activity at 8 weeks as compared to baseline. Additional safety and efficacy parameters were also evaluated over the course of the study.

| Activity Intensity[2,3] | Example activities |
|---|---|
| Sedentary (<100 counts) (< 1.5 MET) | • Lying • Standing • Computer work |
| Light (100 -1951 counts) (1.6 - 3.0 MET) | • Washing dishes • Washing windows • Vacuuming |
| Moderate (1952-5724 counts) (3.1 - 6.0 MET) | • Walking • Ascending/descending stairs • Lawn mowing |
| Vigorous (>5724 counts) (> 6.0 MET) | • Slow/fast running • Intense sports |

An exemplary PH-PF subject is shown with percentage of time in sedentary, light and moderate activity when awake. Vigorous activity was not observed.




Abbreviation: MET – Metabolic Equivalents

**Figure 1: Assessment of Physical Activity** was monitored using a tri-axial accelerometer (Actigraph GT9X).[4] Physical activity is measured as counts which can then be converted into an activity intensity. The average of the counts provides a direct measure of overall physical activity. Each minute of the day is converted into an activity intensity allowing the amount of time in sedentary, light, moderate and vigorous activities to be determined as shown in the table.

**Results**:

Statistically and clinically meaningful improvements were observed in moderate and overall activity parameters **(Table 1)**. Subjects on pulsed inhaled nitric oxide (iNO) demonstrated an increase of 8% in moderate activity versus a 26% decrease for subjects on placebo (p=0.04) **(Figure 2A)**. Subjects on iNO showed no decline in their overall activity levels versus a 12% decline for subjects on placebo (p=0.05) **(Figure 2B)**. Clinically meaningful differences were found in both moderate and overall activity that correlate to established MCID in cardiopulmonary disease **(Table 1)**. iNO was well-tolerated with no safety concerns.

**Table 1: Top Line Actigraphy Results of iNO-PF (iNO 30)**

| Activity Parameter (% change) | iNO | Placebo | Statistical and Clinically Meaningful Differences |
|---|---|---|---|
| Moderate Activity | +8% | -26% | • Statistically significant improvement (p=0.04) • Placebo corrected change 34% • MCID 20% (Distribution Method) |
| Overall Activity | +0% | -12% | • Statistically significant improvement (p=0.05) • Placebo corrected change 12% • MCID 5-10% (Distribution Method) |

| Established Actigraphy MCID for Moderate Activity in Cardiopulmonary Disease |
|---|
| • COPD (Anchor Method): 11-23%[5] • COPD based (Distribution Method): 15-29%[6] • Chronic Heart Failure (Anchor Method): 19%[7] |

Abbreviation: MCID – Minimal Clinical Important Difference, COPD – Chronic Obstructive Pulmonary Disease

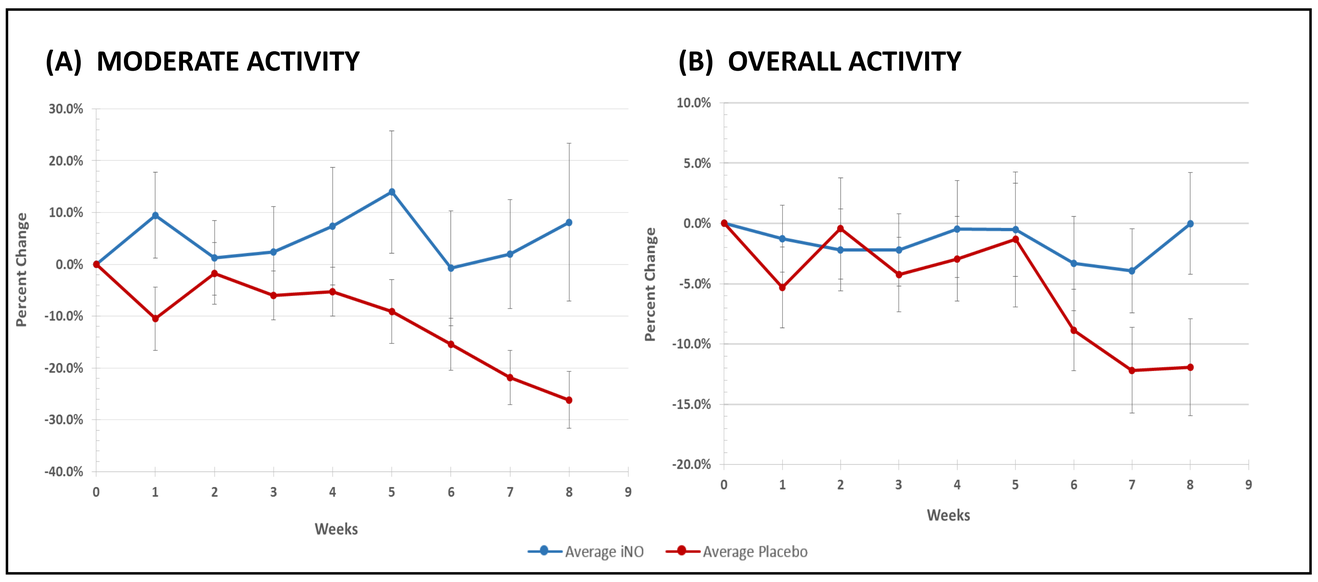



**Figure 2: Weekly Assessment of Activity Parameters** in **(A)** moderate activity and **(B)** overall activity where error bars represent standard errors. In both cases there is clear separation between iNO (—●—) and placebo (—●—) after 4 weeks that reaches statistical significance at week 8.

**Discussion:**

Wearable activity monitoring (actigraphy) can provide continuous objective real-world physical activity data compared to subjective Patient Reported Outcome (PRO) methods of assessment, eliminating recall bias that is associated with activity assessment questionnaires.[8] Numerous studies have shown that the level of physical activity is an established independent predictor of survival and mortality in the general population as well as in patients that have cardiopulmonary diseases, such as pulmonary hypertension, chronic lung diseases (ILD, COPD) and heart failure.[9,10,11,12,13,14,15] Physical activity has also been correlated to a wide range of clinically meaningful outcomes and endpoints such as disease severity, quality of life, functional parameters and exercise capacity **(Table 2)**. MCID determined in iNO-PF are consistent with other cardiopulmonary studies that have reported the clinical significance at 10-20% change in physical activity.[5,6,7] Medical grade activity monitors have been used in over 100 cardiopulmonary trials to assess physical activity as a key endpoint.[16] In addition, there are multiple late stage trials that utilize actigraphy as the primary or key secondary endpoint **(Table 3)**.

**Table 2: Physical Activity Correlation to Outcomes and Endpoints**

| Activity Monitoring Within Disease Area | Correlation of Activity Monitoring to Outcomes and Endpoints |
|---|---|
| PH (PAH, PAH-SSc)[9,10,17] | • Survival • Disease Severity • Exercise Capacity (6MWD) |
| ILD (IPF, NSIP)[10,18,19,20] | • Survival • Quality of Life (SF-12, HADS) • Dyspnea (mMRC) • Lung Function (FVC % pred., DLCO % pred.) • Exercise Capacity (6MWD) |
| COPD[13,14,15] | • Mortality • Hospitalization |
| HF (HFrEF)[9,15,21,22] | • Survival • Quality of Life (MLWHFQ, KCCQ) • NT-proBNP • Key CPX Variables (Peak $VO^2$, $VE/VCO^2$ Slope, OUES) • Functional Class (NYHA) • Exercise Capacity (6MWD) |

**Table 3: Use of Actigraphy and Activity Monitoring in Clinical Studies**

| Phase | Indication | Sponsor | Primary Endpoint | Secondary Endpoints |
|---|---|---|---|---|
| III | Chronic Heart Failure with Reduced Ejection Fraction (sacubitril/valsartan vs enalapril) | Novartis | **Actigraphy** | • Symptom Scores |
| III | COPD (portable oxygen concentrator vs standard of care) | Resmed & Inogen | **Actigraphy** | • SGRQ • Oxygen Usage • HADS |
| IV | PAH (selexipeg vs placebo) | Actelion | **Actigraphy** | • WHO Functional Class • 6MWD • Borg Dyspnea • NT-ProBNP • PAH-Sympact Questionnaire |
| II | Heart Failure with Preserved Ejection Fraction (HFpEF) (macitentan vs placebo) | Actelion | NT-ProBNP | • **Actigraphy** • KCCQ • Time to Worsening |

Abbreviations: PAH: Pulmonary Arterial Hypertension, PAH-SSc: Systemic Sclerosis associated Pulmonary Arterial Hypertension, ILD: Interstitial Lung Disease, IPF: Idiopathic Pulmonary Fibrosis, NSIP: Non-Specific Interstitial Pneumonia, COPD: Chronic Obstructive Pulmonary Disease, HF: Heart Failure, HFrEF: Heart Failure with reduced Ejection Fraction, 6MWD: 6 Minute Walk Distance, SF-12: 12-item Short Form Survey, HADS: Hospital Anxiety and Depression Scale, mMRC: Modified Medical Research Council, FVC: Forced vital capacity, DLCO: Diffusing capacity of the lungs for carbon monoxide, MLWHFQ: Minnesota Living with Heart Failure Questionnaire, KCCQ: Kansas City Cardiomyopathy Questionnaire, NT-proBNP: N-terminal pro b-type natriuretic peptide, $VO^2$: Exercise oxygen uptake, $VE/VCO^2$: Ventilatory equivalent for carbon dioxide, OUES: oxygen uptake efficiency slope, SGRQ: St. .George's Respiratory Questionnaire

**Conclusion:**

**The results of the iNO-PF study has shown both clinically and statistically meaningful benefit in moderate and overall activity as compared to placebo over eight weeks. The determined MCID for physical activity is consistent with other cardiopulmonary disease. The advantage of a continuous quantitative assessment of physical activity by actigraphy, as well as its precedence in prior and ongoing studies, supports its role as a primary regulatory endpoint in subjects with PH-PF.**

References: 1. Vainshelboim, Baruch, et al. "Physical activity and exertional desaturation are associated with mortality in idiopathic pulmonary fibrosis." Journal of clinical medicine 5.8 (2016): 73. 2.Loprinzi, Paul D., et al. "The relationship of actigraph accelerometer cut-points for estimating physical activity with selected health outcomes: results from NHANES 2003–06." Research quarterly for exercise and sport 83.3 (2012): 422-430. 3.Pugh, Meredith E., et al. "Physical activity limitation as measured by accelerometry in pulmonary arterial hypertension." Chest 142.6 (2012): 1391-1398. 4.Actigraph LLC Pensacola, FL, USA 5.Teylan, Merilee, et al. "Physical activity in COPD: Minimal clinically important difference for medical events." Chronic Respiratory Disease 16 (2018): 1479973118816424. 6.Demeyer, Heleen, et al. "The minimal important difference in physical activity in patients with COPD." PloS one 11.4 (2016): e0154587. 7.Shoemaker, Michael J., et al. "Analysis of daily activity data from implanted cardiac defibrillators: the minimum clinically important difference and relationship to mortality/life expectancy." (2012). 8.Dashiell-Aje, Ebony Ph D. Clinical Outcome Assessments Staff, Office of New Drugs, Center for Drug Evaluation and Research, U.S. Food and Drug Administration, " Actigraphy-based Clinical Study Endpoints: A Regulatory Perspective " ww2.amstat.org/meetings/biopharmworkshop/2017/onlineprogram/ViewPresentation.cfm?file=300529.pdf. 9.Ulrich, Silvia, et al. "Wrist actigraphy predicts outcome in patients with pulmonary hypertension." Respiration 86.1 (2013): 45-51.10.Bahmer, Thomas, et al. "Prognosis and longitudinal changes of physical activity in idiopathic pulmonary fibrosis." BMC pulmonary medicine 17.1 (2017): 104. 11.Nishiyama, Osamu, et al. "Physical activity in daily life in patients with idiopathic pulmonary fibrosis." Respiratory investigation 56.1 (2018): 57-63. 12.Waschki, Benjamin, et al. "Physical activity is the strongest predictor of all-cause mortality in patients with COPD: a prospective cohort study." Chest 140.2 (2011): 331-342. 13.Vaes et al, Vaes, Anouk W., et al. "Changes in physical activity and all-cause mortality in COPD." European Respiratory Journal (2014): erj00232-2014.14.Garcia-Aymerich, Judith, et al. "Regular physical activity reduces hospital admission and mortality in chronic obstructive pulmonary disease: a population based cohort study." Thorax 61.9 (2006): 772-778. 15.Walsh, John T., et al. "Relation of daily activity levels in patients with chronic heart failure to long-term prognosis." American Journal of Cardiology 79.10 (1997): 1364-1369. 16. Clinical Trials.gov, NIH U.S. National Library of Medicine, 29 February 2000, clinicaltrials.gov/. 17.Mainguy, Vincent, et al. "Assessment of daily life physical activities in pulmonary arterial hypertension." PLoS One 6.11 (2011): e27993. 18.Bahmer, Thomas, et al. "Clinical correlates of reduced physical activity in idiopathic pulmonary fibrosis." Respiration91.6 (2016): 497-502. 19.Wickerson, Lisa, et al. "Physical activity profile of lung transplant candidates with interstitial lung disease." Journal of cardiopulmonary rehabilitation and prevention 33.2 (2013): 106-112. 20.Wallaert, Benoit, et al. "Physical Activity in Daily Life of Patients With Fibrotic Idiopathic Interstitial Pneumonia" Chest 144.5 (2013): 1652 – 1658. 21.Witbrodt, Bradley C., et al. "Ambulatory Actigraphy Monitoring of Patients with Heart Failure with Reduced Ejection Fraction Predicts 6-Minute Walk Distance." Journal of the American College of Cardiology 69.11 Supplement (2017): 744.
22.Snipelisky, David, et al. "Accelerometer-Measured Daily Activity in Heart Failure With Preserved Ejection Fraction Clinical Perspective: Clinical Correlates and Association With Standard Heart Failure Severity Indices." Circulation: Heart Failure 10.6 (2017): e003878.