MVPA Reflects Life Participation In Patients Using INOpulse Therapy

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Introduction: Fibrotic interstitial lung disease (fILD) includes a variety of disorders, the largest of which is Idiopathic Pulmonary Fibrosis. fILD often manifests in hypoxemia, impaired functional status and reduced physical activity. The FDA's "Idiopathic Pulmonary Fibrosis - The Voice of the Patient Report" highlights the impact of this disease on a patient's daily life, including the severe impact it has on their ability to perform activities of daily living, such as walking, climbing stairs, household chores, etc (**Figure 1**).

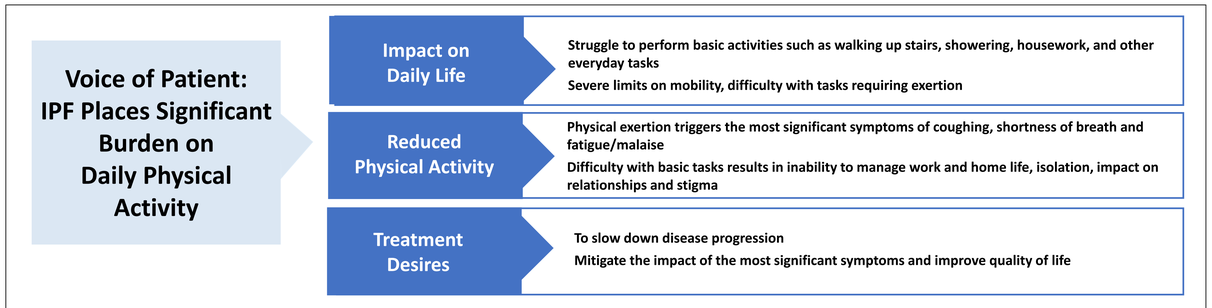


Figure 1: "Idiopathic Pulmonary Fibrosis - The Voice of the Patient Report", US FDA - March 2015[1], captures the impact of IPF on a patient's daily life and their ability to conduct activities of daily living

The World Health Organization has proposed an International Classification on Functioning (ICF) that identifies two distinct components of function: Capacity and Performance[2]. Capacity reflects the ability to do a task in a controlled environment. Performance reflects function in daily life. An example of a Capacity measure is the 6-minute walk test (6MWT).

Measurement of performance provides insight into individual behaviors, barriers to physical activity and the impact of disease on daily physical function. An example of a Performance measure is activity with an intensity in the range of Moderate to Vigorous measured with an accelerometer (**Figure 2**). The assessment of exercise capacity and physical performance are integral to clinical evaluations in PH. It has been suggested that in the fILD population, both capacity and performance should be assessed, in that while the 6MWT accurately assesses capacity at a single point in time, it does not capture physical activity patterns, including sedentary behavior and light activity[3].

Objectives: To determine if wearable activity monitoring (actigraphy) can provide clinically meaningful data sensitive to functional change after treatment with pulsed inhaled nitric oxide (iNO) in patients with fILD.

Methods: The iNO-PF study was designed to assess the safety and clinical benefit of inhaled nitric oxide (iNO) in fILD patients on oxygen therapy. A Phase 2 double blind, randomized controlled study with two independent cohorts of inhaled nitric oxide at either iNO30 (30 mcg/kg IBW/hr) or iNO45 (45 mcg/kg IBW/hr) vs. placebo for 2 to 4 months respectively, were performed. A wrist-worn medical grade activity monitor (Actigraph Pensacola, FL) assessed activity levels. The endpoint of minutes per day of moderate to vigorous physical activity (MVPA) was compared to the activity domain of the St. George's Respiratory Questionnaire (SGRQ) via an anchoring analysis.

Results: Patients on iNO30 and iNO45 demonstrated a 7.5 minute/day placebo corrected benefit in MVPA at month 2, with the iNO45 dose demonstrating a 14 minute/day (p=0.02) placebo-corrected benefit at month 4 (**Figure 3**). At month 4, iNO45 also demonstrated directional improvement in the SGRQ Total, Activity and Impact domain scores (3.3, 4.8 and 5.7-points) respectively. An anchoring analysis, conducted between MVPA and the Activity domain in SGRQ, demonstrated consistency between the two parameters (**Figure 4**).

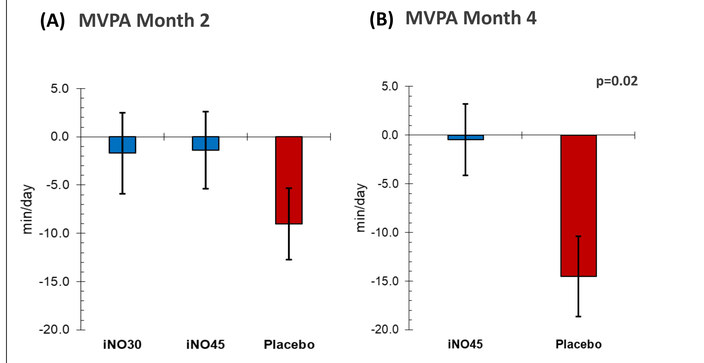


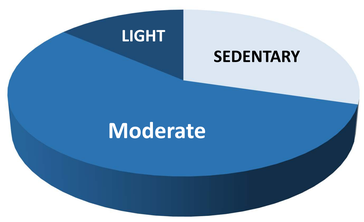
Figure 3: Subjects on iNO30 and iNO45 generally maintained their level of activity, while subjects on placebo declined in their activity levels. **(A)** Subjects on iNO demonstrated 7.5 min/day (~10%) benefit over placebo in MVPA after 2 months of treatment. **(B)** Subjects on iNO demonstrated an increased benefit in MVPA after 4 months of treatment of 14 min/day (20%). MVPA is a measure of moderate and vigorous activities combined)

- Data points and error bars = mean and standard error
- Month 2 analysis based on change from Week 1 to Week 8 and pooled placebo ; Month 4 analysis based on change from Month 1 to Month 4
- p-value based on t-test on available data (exploratory endpoint; not adjusted for multiplicity)

(A)

Voice of Patient (VOP) Daily Physical Activities[1]	MET Range[4]	Activity Intensity[5,6]		
		Sedentary (<1.5 MET)	Light (1.6-3.0 MET)	Moderate (3.1-6.0 MET)
Walking	2.0 – 5.0		X	X
Climbing stairs	3.5 – 6.0			X
Personal Care	1.5 – 2.5	X	X	
Household Chores and Cleaning	1.8 – 6.5	X	X	X
Exercise and Hobbies	1.8 – 6.0		X	X
Socializing	1.3 – 3.0	X	X	

(B)



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

Figure 2: (A) Activities of daily living that reflect life performance as reported in the Voice of Patient, and their associated metabolic equivalent (MET) and activity intensity **(B)** Exemplary distribution of subject activity intensity captured via actigraphy in iNO –PF; subjects spent majority of their waking hours in light and moderate activity.

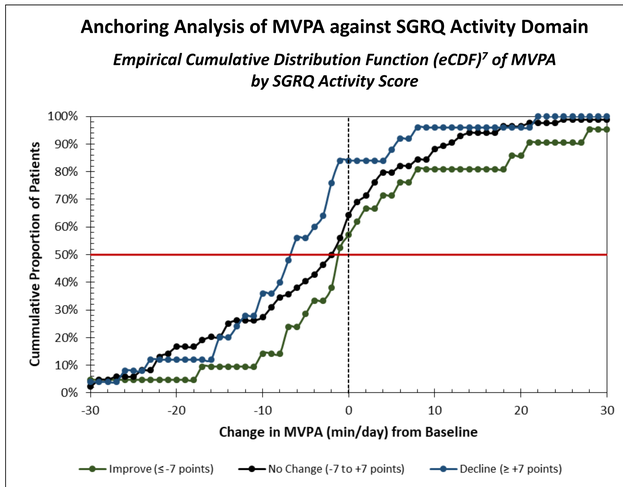


Figure 4: Anchoring analysis was conducted for MVPA using the Activity domain of SGRQ. SGRQ-Activity measures impact to the subject's activity levels due to respiratory symptoms and provides an appropriate anchor to assess the clinical relevance of the changes seen in MVPA.

The change in MVPA for all subjects at Months 2-4 were categorized based on their individual change in SGRQ-Activity. A change of 7 points in SGRQ-Activity was used to separate subjects into improvers, decliners and no change. The cumulative distribution for change in MVPA was calculated for each of the groups (improvers, decliners, and no change).

Subjects categorized as improvers and no change show little difference in their cumulative distribution curves, while there is a clear separation for decliners, with an estimated difference between decliners and no change of 4.8 min/day (based on the 50th percentile).

Conclusion: INOpulse was well tolerated with no significant safety findings, with the iNO45 dose providing compelling benefits in both MVPA and SGRQ compared to placebo in this small study. The anchoring analysis further supported the consistency between the parameters and supported the clinical relevance of the observed benefit. The results of these Phase 2 cohort data support progressing the iNO45 dose into the **REBUILD** registrational Phase 3 placebo-controlled study and allow MVPA to be utilized as the primary endpoint (**Figure 5**).

Figure 5: REBUILD Phase 3 Study Design, Patient Population and Key Endpoints

REBUILD

Phase 2 results support progressing the iNO45 dose into the registrational Phase 3 REBUILD study now underway and actively recruiting at multiple sites in North America (NCT03267108)

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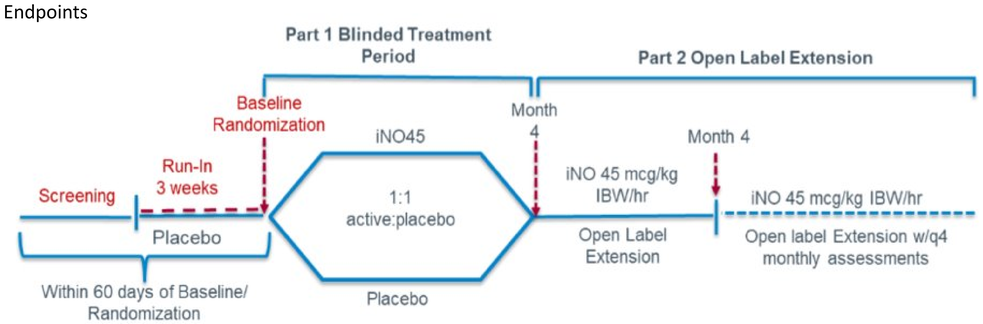

Eligible Patient Population	Key Study Endpoints

Diagnosed with pulmonary fibrosis associated with one of the following conditions:
• **Major IIPs (idiopathic interstitial pneumonias)**
  ○ Idiopathic pulmonary fibrosis, Idiopathic nonspecific interstitial pneumonia, Respiratory bronchiolitis-interstitial lung disease, Desquamative interstitial pneumonia, Cryptogenic organizing pneumonia, Acute interstitial pneumonia
• **Rare IIPs**
  ○ Idiopathic lymphoid interstitial pneumonia, Idiopathic pleuroparenchymal fibroelastosis
• **Unclassifiable idiopathic interstitial pneumonias**
  ○ Chronic hypersensitivity pneumonitis, Occupational lung disease
• **Connective Tissue Disease associated with IPF (CTD-ILD)**
• **Interstitial Pneumonia with Autoimmune Features (IPAF)**
	Actigraphy
	• MVPA
	• Overall activity
	Patient Reported Outcomes
	• UCSD Shortness of Breath Questionnaire
	• SGRQ – Total, Activity and Impact domains
	• PROMIS – FACTT-Fatigue & Physical Function
	• Patient Global Impression of Severity & Patient Global Impression of Change
	Safety
	• Treatment emergent Adverse Events (AEs)
	• Symptomatic rebound
	• All-cause mortality

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