Actigraphy as a clinically meaningful endpoint to detect change after treatment with inhaled NO (30mcg/kg-IBW/hr) in patients at risk of Pulmonary Hypertension associated with Pulmonary Fibrosis

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Introduction:

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. There are currently no approved therapies to treat PH-PF and no established regulatory endpoints. The FDA's "Idiopathic Pulmonary Fibrosis - The Voice of the Patient Report"[1] highlights the impact of this disease on a patient's daily life (**Figure 1**), including the severe impact it has on their ability to perform activities of daily living, such as walking, climbing stairs, household chores, etc. Wearable activity monitoring (actigraphy) can provide continuous, objective, real-world physical activity data of activities of daily living that are relevant to patients.

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). To evaluate if actigraphy could serve as a regulatory endpoint for future pivotal studies.

Methods:

iNO-PF Cohort 1 is a double-blind, placebo-controlled Phase 2b study assessing the safety and efficacy of iNO, delivered by the INOpulse® delivery system, at a dose of 30mcg/kg-IBW/hr (iNO30) in subjects at risk of PH-PF. Subjects were randomized to receive iNO30 (23 subjects) or placebo (18 subjects) for 8 weeks of blinded treatment before entering an open label extension study (OLE). 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.

(A)

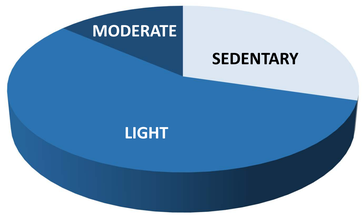
Voice of Patient: IPF Places Significant Burden on Daily Physical Activity

Impact on Daily Life	**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**
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	**To slow down disease progression** **Mitigate the impact of the most significant symptoms and improve quality of life**

(B)

Voice of Patient (VOP) Daily Physical Activities[1]	MET Range[2]	Activity Intensity[3,4]		
		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	

(C)



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

Figure 1: (A) "Idiopathic Pulmonary Fibrosis - The Voice of the Patient Report", US FDA - March 2015, captures the impact of IPF on patient's daily life and their ability to conduct activities of daily living **(B)** Activities of daily living that are impacted by the disease, as reported in the Voice of Patient, and their associated metabolic equivalent (MET) and activity intensity **(C)** Exemplary distribution of subject activity intensity captured via actigraphy in iNO –PF; subjects spent majority of their waking hours in light and moderate activity.

Results:

Statistically and clinically meaningful improvements were observed in moderate and overall activity parameters. Subjects on iNO demonstrated an increase in moderate to vigorous activity (MVPA) versus placebo (p=0.04) as well as no decline in their overall activity levels versus a 12% decline for subjects on placebo (p=0.05) (**Figure 2**). Responder analysis (**Figure 3**) further supported the top-line results, with up to 60% of subjects on iNO demonstrating improvement, compared to 85% of subjects on placebo declining. During OLE, subjects who were on iNO maintained their activity levels while subjects who were on placebo saw a trend reversal from deterioration to maintenance (**Figure 4**). iNO was well-tolerated with no safety concerns.

Percent Change from Baseline after 8 Weeks of Blinded Treatment

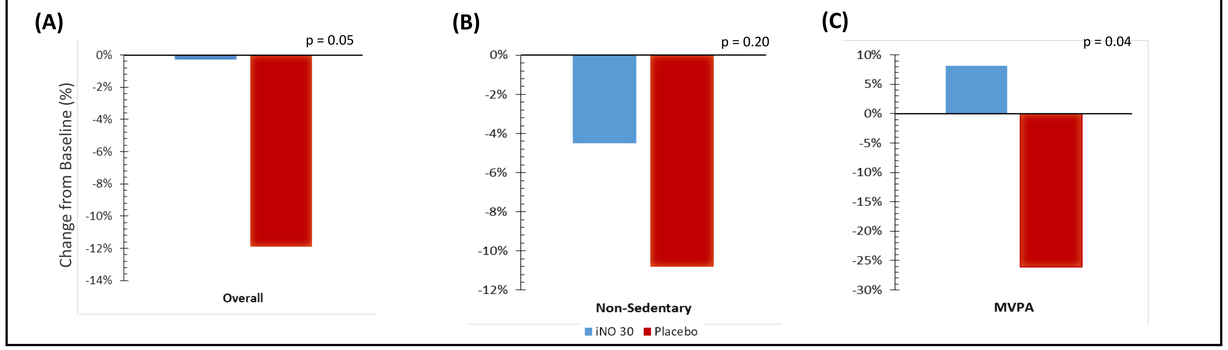


Figure 2: Subjects on pulsed inhaled nitric oxide (iNO) demonstrated a placebo corrected improvement of **(A)** 12% in overall activity, **(B)** 6% in non-sedentary activity and **(C)** 34% in MVPA. Percent change is calculated as absolute change/baseline, e.g. Δ MVPA (minutes)/Baseline MVPA (minutes). Statistical analysis was conducted for active vs. placebo via student t.test at week 8 on available data.

Responder Analysis Verifies Clinically Important Improvement on iNO Compared to Placebo

Change from Baseline	Overall		Non-Sedentary		MVPA		
	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**

Figure 3: Actigraphy responder analysis shows 39-62% of subjects on iNO improved with 8-23% demonstrating clinically significant improvement. By comparison, 85% of subjects on placebo decline with 71% demonstrating clinically significant decline in MVPA. ±15% change from baseline is considered clinically significant.

Subjects Randomized to Placebo Transition from Decline to Maintenance on OLE

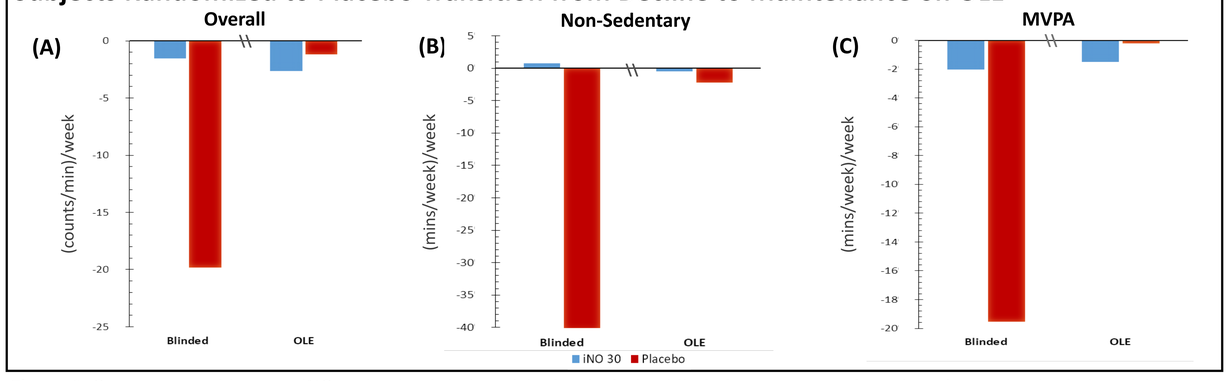


Figure 4: On average, subjects on iNO maintained their activity levels during blinded treatment and continued to maintain their activity levels during open label treatment (OLE). By comparison, subjects on placebo declined in their activity levels during blinded treatment, but reversed to maintaining their activity levels when they transitioned to open label treatment on iNO.

Conclusion:

Results of Cohort 1 of the iNO-PF study demonstrated clinically and statistically meaningful benefit in multiple activity parameters over eight weeks of iNO treatment. The benefits was consistent during open label extension (OLE), where subjects who were on iNO maintained their activity levels while subjects who were on placebo saw a trend reversal from deterioration to maintenance. iNO was well-tolerated with no safety concerns. This quantitative assessment of physical activity by actigraphy allows for a direct and continuous measurement of activities of daily living that are relevant to patients. The results of Cohort 1 have allowed MVPA to be utilized as the primary regulatory endpoint in the pivotal Phase 3 Cohort of this ongoing iNO-PF study.

REFERENCES: 1 US Food and Drug Administration. The Voice of Patient – Idiopathic Pulmonary Fibrosis. Retrieved from https://www.fda.gov/downloads/forindustry/userfees/prescriptiondruguserfee/ucm440829.pdf Effective March 2015. Accessed January 30, 2019. 2 Ainsworth BE, Haskell WL, Herrmann SD, Meckes N, Bassett Jr DR, Tudor-Locke C, Greer JL, Vezina J, Whitt-Glover MC, Leon AS. 2011 Compendium of Physical Activities: a second update of codes and MET values. Med Sci Sports Exerc. 2011;43(8):1575-81. 3 Loprinzi PD, Lee H, Cardinal BJ, Crespo CJ, Andersen RE, Smit E. The relationship of actigraph accelerometer cut-points for estimating physical activity with selected health outcomes: results from NHANES 2003–06. Res Q Exerc Sport. 2012;83(3):422-30. 4 Ainsworth BE, Haskell WL, Herrmann SD, Meckes N, Bassett Jr DR, Tudor-Locke C, Greer JL, Vezina J, Whitt-Glover MC, Leon AS. 2011 Compendium of Physical Activities: a second update of codes and MET values. Med Sci Sports Exerc. 2011;43(8):1575-81.