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

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Introduction:

Pulmonary fibrosis (PF) is made up of a variety of fibrotic lung diseases, the largest of which is IPF (Idiopathic Pulmonary Fibrosis). Pulmonary hypertension frequently complicates pulmonary fibrosis (PH-PF) and is associated with impaired functional capability and significantly reduced life expectancy. Patients with PH-PF have significantly lower physical activity compared to healthy subjects and have poorer health outcomes. There are currently no approved therapies to treat PH-PF as systemic vasodilators used in Pulmonary Arterial Hypertension (PAH) have proven to be ineffective in PH-PF. iNO is a well-established and approved vasodilator for the acute treatment of persistent pulmonary hypertension of the newborn. The INOpulse targeted delivery may ameliorate ventilation-perfusion (V/Q) mismatch, thereby maintaining and possibly improving oxygen.

Methods:

The study was designed to assess the safety and clinical benefit of iNO 30 in subjects with either low or intermediate/high risk of PH associated with PF. The objective was for the identification and selection of the most appropriate clinically meaningful endpoint for pivotal studies. Subjects in the first cohort (Cohort 1) were randomized to receive iNO 30 or placebo 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. Continuous activity monitoring provides a direct, objective and autonomous measure of moderate to vigorous physical activity (MVPA) such as walking, going up the stairs, housework/yardwork and other activities of daily living. Additional safety and efficacy parameters were also evaluated over the course of the study.

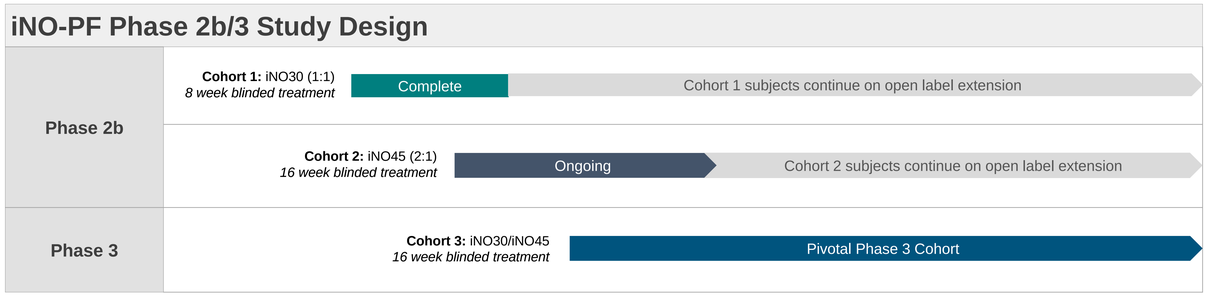

Figure 1: iNO-PF Study Design allows for a seamless transition from Phase 2b (Cohorts 1 and 2) into a pivotal Phase 3 Cohort. Dose for Phase 3 to be finalized based on the results from the ongoing Cohort 2.

Results:

There were 41 patients recruited into the study, of whom 23 received iNO 30 and 18 received placebo. Evaluable subjects on iNO demonstrated a 34% improvement in MVPA as compared with placebo (p=0.04). Statistically significant improvements were also observed in additional clinically meaningful activity parameters (overall activity and calories expended). Improvements in physical activity were supported by improvement in oxygen saturation, consistent with INOpulse's ability to target delivery to the well ventilated alveoli. Subjects on open label extension saw continued benefit on treatment, with subjects who transitioned from placebo to active seeing a trend reversal from deterioration to improvement in both MVPA and overall activity.

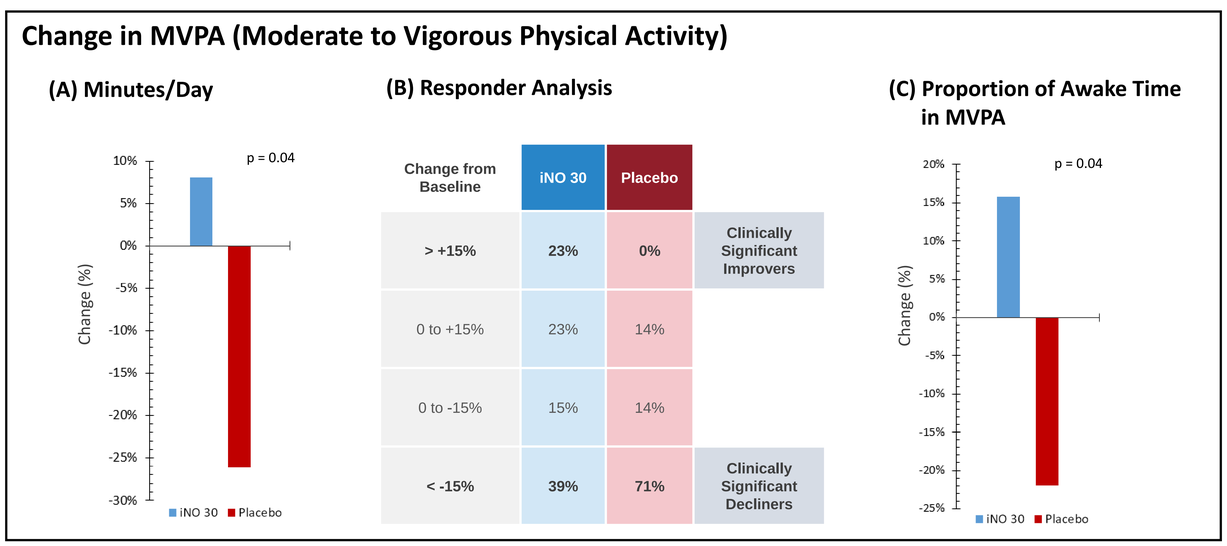

Figure 2: (A) Subjects on pulsed inhaled nitric oxide (iNO) demonstrated an increase of 8% in minutes of moderate to vigorous activity (MVPA) versus a 26% decrease for subjects on placebo (p=0.04). **(B)** 23% of subjects on iNO had a clinically significant improvement in MVPA as compared to 0% of subjects on placebo. 39% of subjects on iNO had a clinically significant decline in MVPA as compared to 71% of subjects on placebo. Clinically significant change is considered >15% from baseline. **(C)** Subjects on iNO demonstrated an increase of 16% in the proportion of awake time spent in MVPA versus a 22% decrease for subjects on placebo (p=0.04).

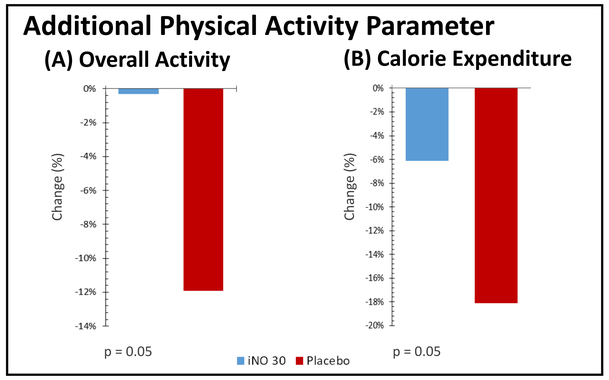

Figure 3: (A) Subjects on iNO maintained their overall activity versus a 12% decrease for subjects on placebo (p=0.05). **(B)** Subjects on iNO demonstrated a decrease of 6% in calories expended versus an 18% decrease for subjects on placebo (p=0.05).

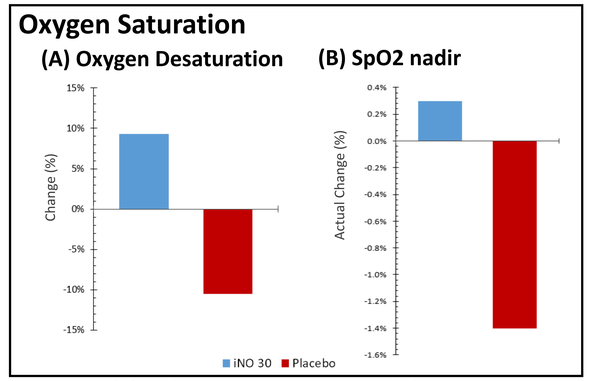

Figure 4: (A) Subjects on iNO improved by 9% in oxygen desaturation, while subjects on placebo deteriorated by 11 %. **(B)** Subjects on iNO improved their absolute SpO2 nadir by 0.3% while subjects on placebo deteriorated by 1.4%.

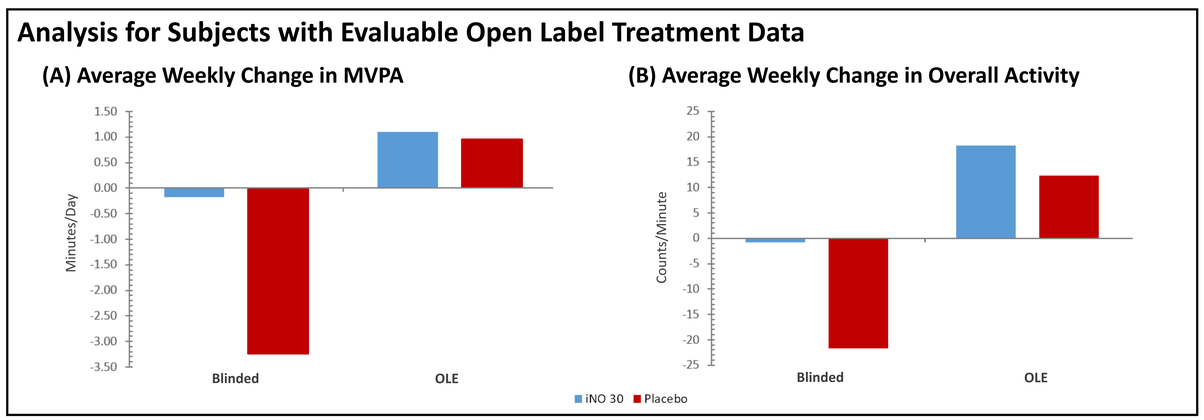

Figure 5: Upon completion of blinded treatment, subjects continued on open label extension (OLE). **(A)** During open label extension subjects saw an average weekly increase of 1 minute/day in MVPA. During blinded treatment, subjects on iNO remained stable while subjects on placebo saw an average weekly decrease of 3 minutes/day**. (B)** During open label extension subjects saw an average weekly increase of 15 counts/min in overall activity. During blinded treatment, subjects on iNO remained stable while subjects on placebo saw an average weekly decrease of 22 counts/min. Overall activity is measured in counts, a magnitude of a subject's daily movement as measured via tri-axial acceleration.

Safety Summary

- Pulsed Inhaled Nitric Oxide was well tolerated at the iNO 30 dose in Cohort 1
- Incidence of AEs and SAEs was low in both active and placebo and was balanced across both groups
- All SAEs were reported as unrelated to the Study drug
- There were no unexpected AEs or Serious Unexpected Suspected Adverse Reaction (SUSARs) reported

Conclusion:

iNO 30 was safe and well tolerated and provided clinically and statistically meaningful improvements in MVPA, overall activity and calories expended as compared to placebo. The continuous and quantitative assessment provided by actigraphy allows it to serve as a primary regulatory endpoint indicative of a clinically meaningful improvement in subjects with PH-PF. The continuous and quantitative assessment provided by actigraphy provides a direct measure of patients functional ability in the home environment. The recognition of this coupled with the results of this study will enable it to serve as the primary endpoint for a pivotal phase 3 registration study.

Summary of iNO-PF Cohort 1 Clinical Results

- Statistically significant placebo corrected improvement of 34% in MVPA;
- Additional activity parameters (proportion of awake time in MVPA, overall activity and calories expended) also show statistically significant benefit
- INOpulse targeted delivery improves oxygen saturation during exercise
- Consistent improvement in MVPA and overall activity for subjects on open label extension, with subjects who transitioned from placebo to active seeing a trend reversal from deterioration to improvement
- Pulsed inhaled NO was safe and well tolerated
- MVPA is being progressed as the primary endpoint in the pivotal Phase 3 cohort