A Subgroup analysis from the randomized, double-blind, placebo-controlled study of inhaled nitric oxide (iNO) in subjects at risk of Pulmonary Hypertension associated with Pulmonary Fibrosis (PH-PF)

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Introduction:
Pulmonary fibrosis (PF) consists of a variety of fibrotic lung diseases, the largest of which is IPF (Idiopathic Pulmonary Fibrosis). Pulmonary hypertension frequently complicates PF and is associated with impaired functional capability and significantly reduced life expectancy. There are currently no approved therapies to treat PH-PF.

Objectives:
Inhaled nitric oxide (iNO) at a dose of 30 mcg/kg IBW/hr has recently been reported to improve moderate to vigorous activity (MVPA) levels as measured by actigraphy in a randomized, placebo-controlled study. This is a subgroup analysis exploring whether any phenotypes drove the efficacy signal.

Methods:
Subjects were randomized to receive iNO 30 (n=23) or placebo (n=18) for 8 weeks of blinded treatment (see **Figure 1** for study design). A wrist-worn activity monitor was used to assess changes in daily activity at 8 weeks. The placebo corrected change in the iNO group for the overall study population is compared with the change in specific subgroups including those with greater probability of having PH, IPF diagnosis, an FVC >50% and 6MWD ≤300m.

Results:
Table 1 provides the patient demographics for Cohort 1. Baseline characteristics were well balanced between the groups with the exception of a higher percentage of IPF subjects in the active arm compared to the placebo arm. Top line results showed clinically and statistically significant improvement in MVPA for the overall population (**Figure 2**). Other actigraphy parameters and oxygen saturation (data not shown) supported the overall clinical benefit seen in Cohort 1. Subgroup analysis (**Figure 3**) showed iNO provided benefit for both intermediate/high and low probability of PH groups. Subjects with underlying IPF, baseline FVC > 50%, or baseline 6MWD ≤300 m had greater changes in MVPA compared to the overall population.

Table 1: Demographic Summary of Subjects randomized to iNO 30 (n=23) or placebo (n=18) for 8 weeks of blinded treatment in Cohort 1 of iNO-PF Study

	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 ± standard deviation)	293.8 ± 87.9	271.4 ± 91.3	284.0 ± 89.0

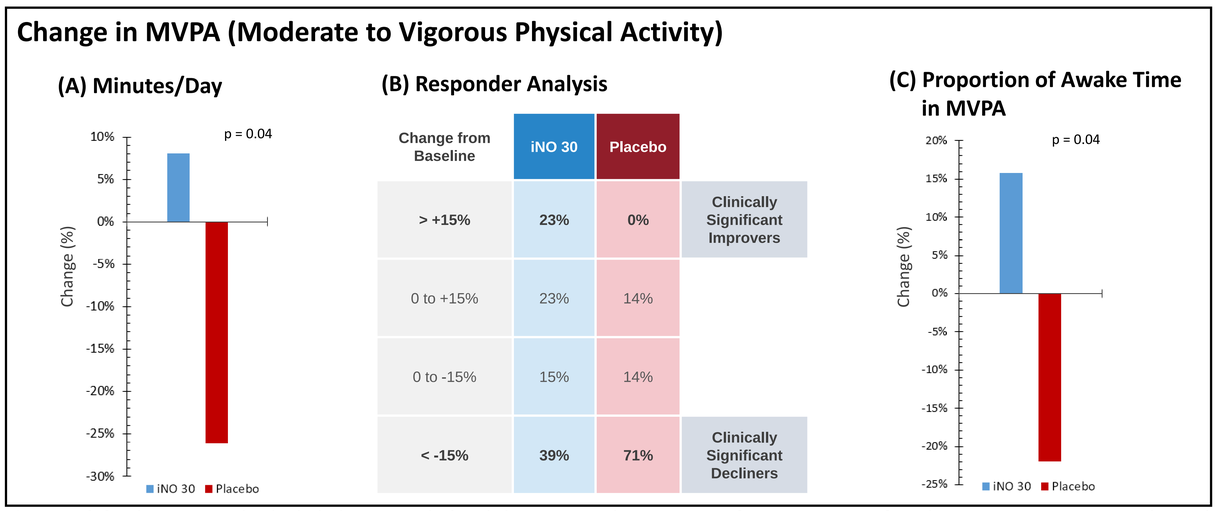

Figure 2: (A) Subjects on pulsed inhaled nitric oxide (iNO) demonstrated an increase of 8% in minutes of moderate to vigorous activity (MVPA) versus a 26% decrease for subjects on placebo (p=0.04). **(B)** 23% of subjects on iNO had a clinically significant improvement in MVPA as compared to 0% of subjects 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). Analysis based on 27 evaluable subjects.

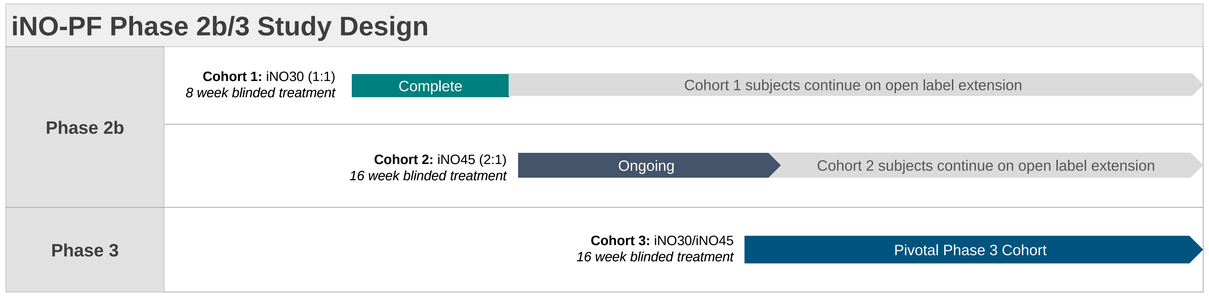

Figure 1: iNO-PF Study Design allows for a seamless transition from Phase 2b (Cohorts 1 and 2) into a pivotal Phase 3 Cohort. Dose for Phase 3 to be finalized based on the results from the ongoing Cohort 2.

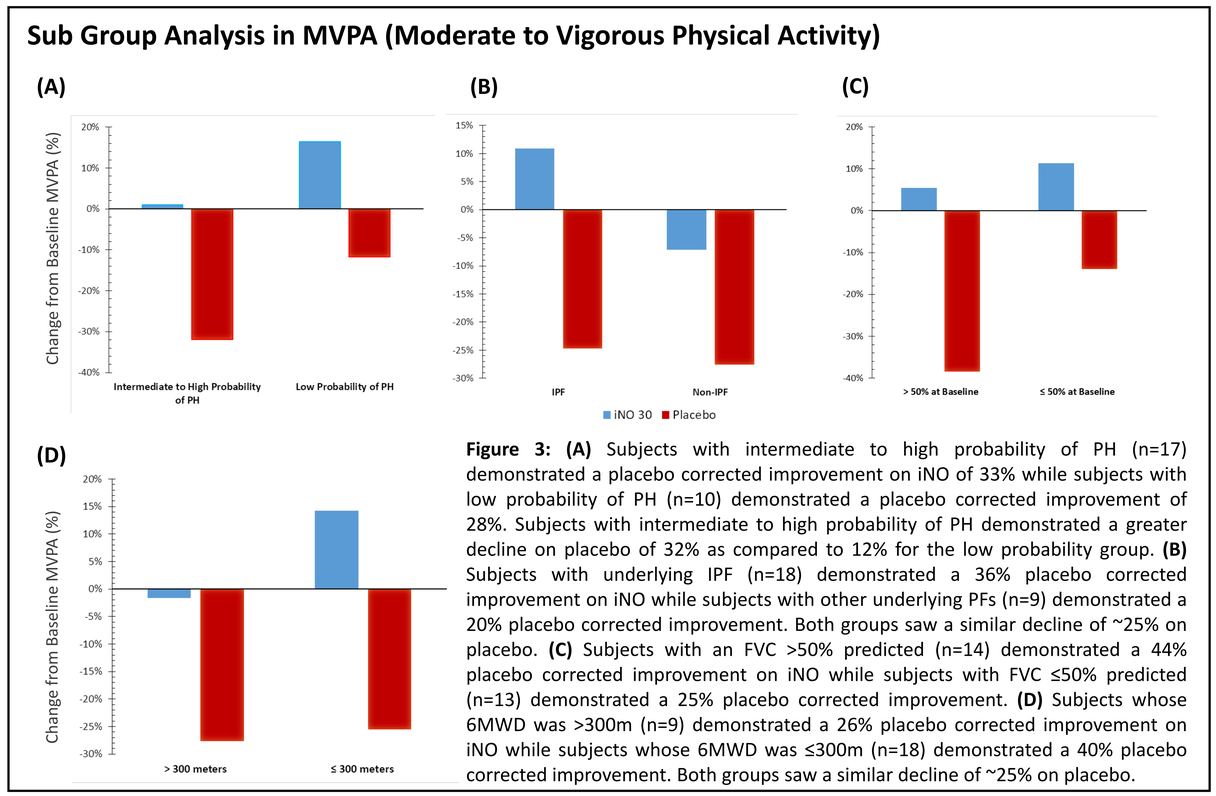

Figure 3: (A) Subjects with intermediate to high probability of PH (n=17) demonstrated a placebo corrected improvement on iNO of 33% while subjects with low probability of PH (n=10) demonstrated a placebo corrected improvement of 28%. Subjects with intermediate to high probability of PH demonstrated a greater decline on placebo of 32% as compared to 12% for the low probability group. **(B)** Subjects with underlying IPF (n=18) demonstrated a 36% placebo corrected improvement on iNO while subjects with other underlying PFs (n=9) demonstrated a 20% placebo corrected improvement. Both groups saw a similar decline of ~25% on placebo. **(C)** Subjects with an FVC >50% predicted (n=14) demonstrated a 44% placebo corrected improvement on iNO while subjects with FVC ≤50% predicted (n=13) demonstrated a 25% placebo corrected improvement. **(D)** Subjects whose 6MWD was >300m (n=9) demonstrated a 26% placebo corrected improvement on iNO while subjects whose 6MWD was ≤300m (n=18) demonstrated a 40% placebo corrected improvement. Both groups saw a similar decline of ~25% on placebo.

Conclusion:
This post hoc subgroup analysis identifies patient phenotypes more likely to respond to iNO. Although limited in sample size, these findings may potentially impact the design and/or analysis of the planned pivotal phase 3 study.

Summary of iNO-PF Cohort 1 Sub-Group Analysis

- Overall group demonstrated a statistically significant placebo corrected improvement of 34% in MVPA and iNO was safe and well-tolerated
- Subjects with intermediate/high probability of PH exhibited greater deterioration on placebo as compared to subjects with low probability of PH, consistent with the reduced life expectancy and quality of life in subjects with associated pulmonary hypertension; both groups demonstrated an average placebo corrected benefit of 30% on iNO
- Subjects with FVC >50% predicted demonstrated increased benefit on iNO indicating reduced lung function may influence the overall benefit provided by pulmonary vasodilation
- Subjects with 6MWD ≤300 meters demonstrated increased benefit on iNO. This therapy can facilitate and enhance the ability to perform activities of daily living that are measured by MVPA; this group also demonstrated placebo corrected improvements of 33 meters in 6MWD and 39 meter% in distance saturation product (6MWD × SpO2 Nadir)