A Randomized, Double-Blind, Placebo-Controlled Study to Assess the Safety and Efficacy of Pulsed, Inhaled Nitric Oxide (iNO) in Subjects at Risk of Pulmonary Hypertension (PH) Associated with Fibrotic Interstitial Lung Disease (fILD) on Long Term Oxygen Therapy

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Background:

Fibrotic interstitial lung disease (fILD) includes a variety of disorders, the largest of which is Idiopathic Pulmonary Fibrosis. Pulmonary hypertension (PH) frequently complicates fILD and is associated with impaired functional capability and significantly reduced life expectancy. Patients with PH-fILD have significantly lower physical activity with poorer health outcomes compared to healthy subjects. There are currently no approved therapies to treat PH-fILD. iNO is a well-established and approved pulmonary vasodilator. iNO, at a dose of 30 mcg/kg-IBW/hr (iNO30) has recently been shown to improve moderate to vigorous physical activity (MVPA) in patients with fILD[1]. The objective of this study was to investigate the effects of a higher dose of iNO45 in patients with fILD to determine the optimal dose to progress into a pivotal Phase 3 Cohort [**Figure 1**].

Methods:

The study was designed to assess safety and clinical benefit of iNO in subjects at low and intermediate/high risk of PH-fILD on supplemental oxygen therapy. Subjects were randomized to receive iNO45 (n=30) or placebo (n=14) for 4 months of blinded treatment. A wrist-worn medical grade activity monitor assessed changes in activity levels at 4 months compared to baseline. The primary endpoint MVPA, reflected measured activities of daily living (ADL). Additional endpoints included the patient reported outcomes (PRO) of SGRQ and UCSD SOBQ. A 5-point change in the UCSD SOBQ and 4-point change in the SGRQ domains are generally regarded as clinically important. An anchoring analysis was conducted between MVPA and the Activity domain of SGRQ using data from Cohorts 1 and 2. Safety and efficacy parameters were also evaluated.

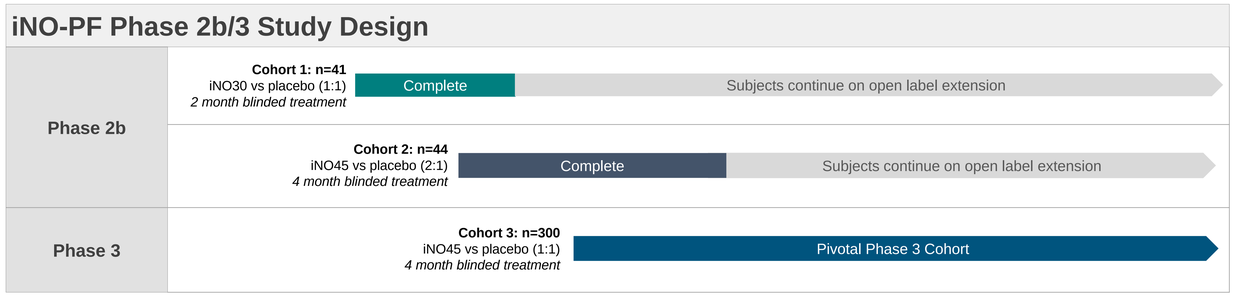


Figure 1: iNO-PF Study Design allows for a seamless transition from Phase 2b (Cohorts 1 and 2) into a pivotal Phase 3 Cohort. Results from Cohort 2 verified the final dose of iNO 45 for the pivotal Phase 3 Cohort.

Results:

There was a statistically significant (p=0.02) 14 minute/day (~20%) placebo corrected benefit of iNO45 in MVPA (walking, stairs, yardwork, etc.). There was also a 7% benefit in overall activity with iNO45 compared to placebo. For both activity parameters, the treatment group remained stable while the group on placebo deteriorated [**Figure 2**]. Clinically significant benefit were reported in the UCSD SOBQ (4.8 points) and the SGRQ Total, Activity and Impact domain scores (3.3, 4.8 and 5.7-points) respectively. Similar to the changes in MVPA, the treatment group remained stable in both UCSD and SGRQ questionnaires, while the placebo group deteriorated [**Figure 3**]. An anchoring analysis, conducted between MVPA and the Activity domain in SGRQ, demonstrated consistency between the two parameters with an estimated minimally important difference (MID) of ~5 minutes per day for MVPA [**Figure 4**]. The results of the clinical trial demonstrated a 14 minute per day benefit after 4 months of treatment. iNO 45 was well tolerated with the number of SAEs being lower in the iNO group compared to placebo (10% vs 21%). No deaths were reported.

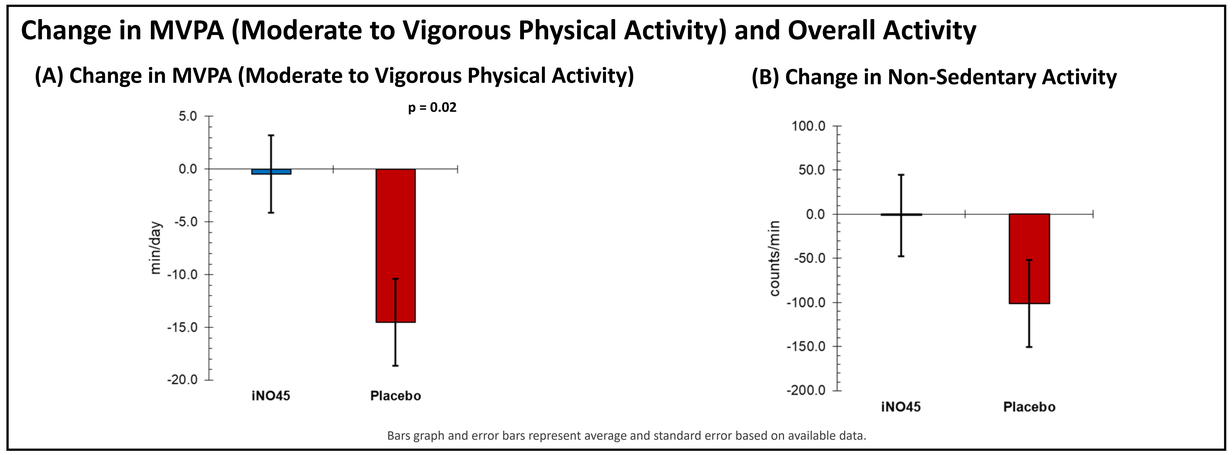


Figure 2: Subjects on iNO45 generally maintained their level of activity, while subjects on placebo declined in their activity levels. **(A)** Subjects on iNO demonstrated 14 min/day (~20%) benefit over placebo in MVPA after 4 months of treatment (p=0.02). **(B)** Subjects on iNO maintained their overall activity versus subjects on placebo who demonstrated ~100 counts/min (~7%) drop in overall activity after 4 months of treatment. Overall activity is a measure of all activities (i.e. MVPA + Light and Sedentary Activity).

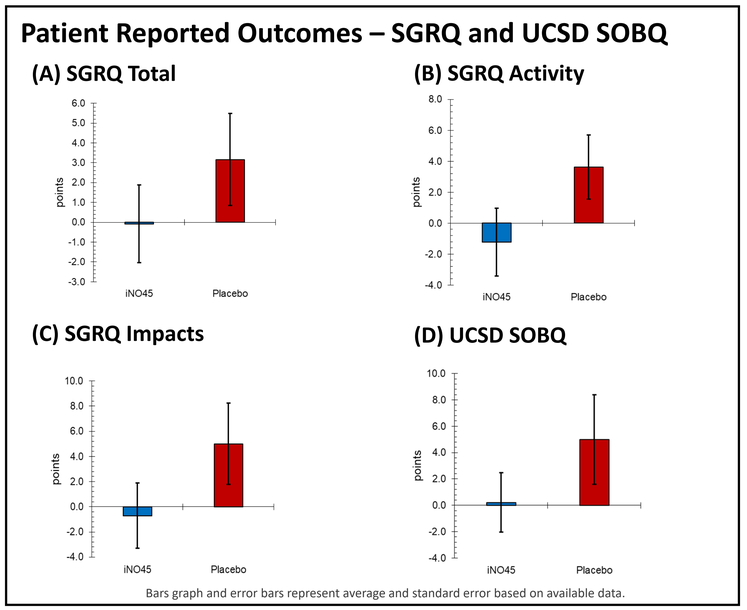
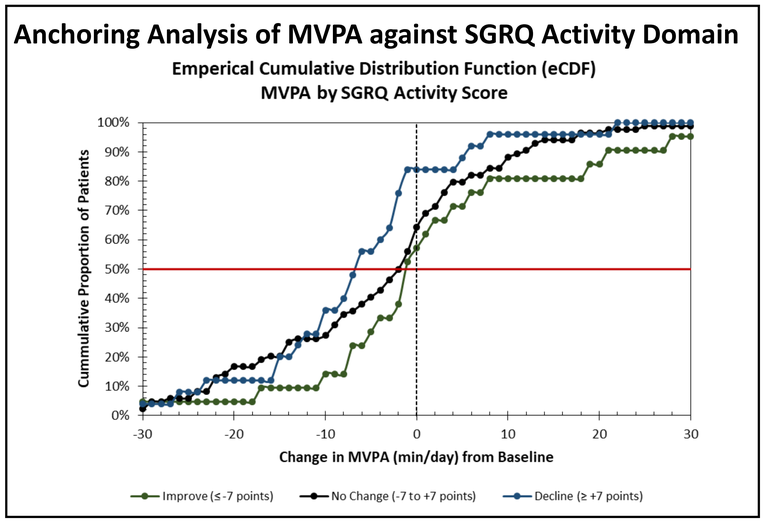


Figure 3: Patient quality of life was measured using the St. George's Respiratory Questionnaire (SGRQ) and UCSD Shortness of Breath Questionnaire. Subjects on iNO45 maintain or improve while subjects on placebo decline, consistent with the results demonstrated with actigraphy. Note: increase in score represents deterioration, with a 4-point change in SGRQ and 5-point change in UCSD typically considered clinically significant. **(A)** SGRQ Total represents overall quality of life, with subjects on iNO45 demonstrating 3.3-point placebo corrected improvement after 4 months. **(B)** SGRQ Activity is a measure of a subjects' ability to conduct activities of daily living, with subjects on iNO45 demonstrating a 4.8-point placebo corrected benefit after 4 months. **(C)** SGRQ Impacts score measures impact on the psychological and social functioning, with subjects on iNO45 demonstrating 5.7-point placebo corrected benefit after 4 months. **(D)** UCSD Shortness of Breath Questionnaire (SOBQ) was utilized to assess the degree of dyspnea when conducting daily activities, a key symptom concerning to patients with pulmonary fibrosis. Subjects demonstrated a 4.8-point placebo corrected benefit.

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[2,3,4] 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).



Safety Summary

- Pulsed Inhaled Nitric Oxide was well tolerated at iNO45 dose in Cohort 1
- Cohort 2 SAE rate after 4 months: iNO 45 (10.0%) vs Placebo (21.4%)
- Overall incidence of AEs was low in both active and placebo and was balanced across both groups

Conclusion

INOpulse was safe and well tolerated, with iNO45 providing clinically meaningful benefits in MVPA and PROs compared to placebo in this small study. The benefit in the objective measurement of activity tracked the benefit observed with the two PROs, with subjects on iNO remaining stable while subjects on placebo deteriorated. Anchoring analysis further supported the consistency between the parameters. The outcomes of this study confirm our previously reported results seen with iNO at a lower concentration of iNO30[1]. iNO45 is progressing into a registrational Phase 3 placebo-controlled study in patients with fibrosing ILD.

References: [1]Nathan, S.D., Flaherty, K.R., Glassberg, M.K., Raghu, G., Swigris, J., Alvarez, R., Ettinger, N., Loyd, J., Fernandes, P., Gillies, H. and Kim, B., 2020. 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) receiving Oxygen Therapy. Chest. [2]Suzuki, A., Kondoh, Y., Swigris, J.J., Ando, M., Kimura, T., Kataoka, K., Yamano, Y., Furukawa, T., Numata, M., Sakamoto, K. and Hasegawa, Y., 2018. Performance of the St George's Respiratory Questionnaire in patients with connective tissue disease associated interstitial lung disease. Respirology, 23(9), pp.851-859. [3]Swigris, J.J., Wilson, H., Esser, D., Conoscenti, C.S., Stansen, W., Leidy, N.K. and Brown, K.K., 2018. Psychometric properties of the St George's Respiratory Questionnaire in patients with idiopathic pulmonary fibrosis: insights from the INPULSIS trials. BMJ open respiratory research, 5(1), p.e000278. [4]Swigris, J.J., Brown, K.K., Behr, J., du Bois, R.M., King, T.E., Raghu, G. and Wamboldt, F.S., 2010. The SF-36 and SGRQ: validity and first look at minimum important differences in IPF. Respiratory medicine, 104(2), pp.296-304.