A Phase 2 Placebo-controlled, Randomized, Double-blind Clinical Study to Assess the Efficacy, Safety and Tolerability of Two Doses of Pulsed, Inhaled Nitric Oxide (iNO) in Patients with WHO Group 1 Pulmonary Arterial Hypertension (PAH)

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Abstract

Rationale: Inhaled nitric oxide is a selective pulmonary vasodilator. Clinical experience suggests that iNO has the potential to treat ambulatory patients with pulmonary hypertension, including those with WHO Group 1 (PAH)

Methods: This was a Phase 2, randomized, placebo-controlled, double-blind study. Patients must have been on at least one PAH therapy and have symptoms of PAH. We report the results of Part 1 (randomization to 16 weeks).
The primary endpoint was change in pulmonary vascular resistance (PVR), and secondary endpoints included change in 6 minute walk distance (6MWD), WHO functional class (FC), and SF-36 Physical component summary (PCS), all from randomization to week 16.
Patients were randomized (in a 1:1:1 ratio) to receive either placebo (N2) or pulsed NO at doses of either 25 or 75 mcg/kg ideal body weight/hr (25 or 75 mcg). iNO was delivered via nasal cannula using the INOpulse device.

Results: 80 subjects were recruited. The majority of subjects were female (79%), white (89%) and had idiopathic PAH (74%). Subjects randomized to placebo had a lower % on long term oxygen therapy (LTOT). At 16 weeks, there were non-statistically significant trends toward lower PVR in the iNO cohorts compared to placebo (see table), and a slight trend toward increased 6MWD in the 75 mcg/kg dose group. Treatment effect was minimal on FC and PCS endpoints.
In exploratory analyses (see table), subjects using LTOT at baseline appeared more adherent to using the device: (retrospectively defined as ≥ 12h/day) 70% vs. 33% not using LTOT. This observation drove non-scheduled, exploratory analyses by LTOT use. In the LTOT users, a placebo controlled decrease in PVR was observed and the 6MWD improved in the 75 mcg dose group. There was a <15% decline on 6MWD in non-LTOT users.
The safety of iNO appeared acceptable: subjects experiencing serious adverse events (SAE) numbered 4 on placebo, 4 in the 25 dose group and 9 in the 75 dose group while drug-related SAE occurred in 0, 1, &1 subject, respectively.

Conclusion: In the ITT population, iNO did not significantly affect the PVR or 6MWD in patients with PAH. Minimal differences were seen for WHO functional class and PCS endpoints. Safety of iNO appeared acceptable. Exploratory analyses suggest settings where increased adherence could be expected, such as use in LTOT, could be a way forward in future studies of iNO in PAH. Phase III trials are in the planning stages.

Background

iNO is a selective pulmonary vasodilator. The mechanism of NO-mediated vasodilation occurs via the activation of soluble guanylate cyclase, the production of cyclic guanosine monophosphate, and subsequent relaxation of vascular smooth muscle. iNO produces pulmonary vasodilation with minimal effect on systemic vascular beds due to its high affinity for hemoglobin and rapid inactivation.

Initial studies of iNO using constant concentrations over the entirety of inspiration consistently demonstrated improvements in pulmonary hemodynamics (mean pulmonary arterial pressure [mPAP] and pulmonary vascular resistance).

Study Design

Placebo-controlled, double-blind, randomized, clinical study.

Objectives (Week 0-16):

- Determine the safety, tolerability, efficacy of two different doses of iNO delivered by a pulsed delivery device in symptomatic subjects with PAH
- Doses of iNO: 25 and 75 mcg/Kg IBW/24h

Primary Endpoint:

- Change in PVR from Baseline to Week 16

Secondary Endpoints:

- Change in 6MWD from Baseline to Week 16
- Time to first clinical worsening event (TTCW)
- Change in WHO Functional Class
- Change in Borg Dyspnea scale
- Change in SF-36 short form version 2 and CAMPHOR

Key Inclusion Criteria:

- WHO Group 1 PAH
- On at least one approved PAH medication and symptomatic from PAH
- 6MWD at least 100 meters and no greater than 450 meters

Key Exclusion Criteria:

- iagnosis of WHO PH Group 2, 3, 4 or 5
- Moderate to severe obstructive or restrictive pulmonary disease
- Patients on CPAP or BiPAP

Demography and PAH Background

	Placebo	25 iNO	75 iNO
N analyzed	26	27	27
Mean age, yrs., (range)	52 (29-75)	56 (32-76)	58 (19-81)
Female	81%	82%	78%
White	89%	85%	93%
PAH Duration (mean & range, yrs.)	5.5 (0.8-17.8)	6.2 (0.4-18.9)	6.2 (0.8-21.3)
PAH Diagnosis (n)			
iPAH	19 (73%)	20 (74%)	20 (74%)
CTD	4	7	7
Other PAH	3	0	0
WHO Class (n)			
I	1	0	0
II	6	6	4
III	19 (73%)	21 (78%)	21 (78%)
IV	0	0	2
LTOT (n & %)	12 (46%)	16 (59%)	21 (78%)

Background PAH Medication

	Placebo	25 iNO	75 iNO
N analyzed	26	27	27
Monotherapy	7 (27%)	3 (11%)	6 (22%)
Dual Therapy	12 (46%)	18 (67%)	14 (52%)
Triple Therapy	6 (23%)	6 (22%)	7 (26%)

Summary of Safety Results

Patients	Placebo	25 iNO	75 iNO
Number of patients	26	27	27
Total Adverse Events	23	22	26
Drug Related AEs	9	10	9
Total Serious Adverse Events	4	4	9
Drug Related SAEs	0	1	1
Deaths	1	0	0
Discontinuation due to AEs	1	1	2

Results

Primary Endpoint PVR (ITT)

PVR (dynes sec.cm^{-5})	Placebo	25 iNO	75 iNO
N analyzed	24	23	24
Baseline (mean)	602	666	663
Change from baseline (mean)	+47	-54	-15
95% CI (change vs placebo)		(-218, 15)	(-177, 53)
P-value (ANOVA)		0.091	0.178
% with average daily use ≥12h	42%	52%	75%

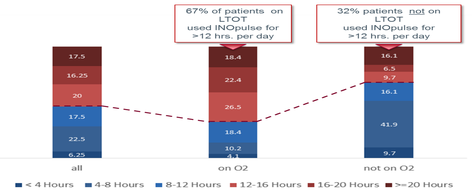
Secondary Endpoint: 6MWD (ITT)

6MWD (m)	Placebo	25 iNO	75 iNO
N analyzed	24	24	23
Baseline (mean)	368	327	301
Change from baseline (mean)	+8	+5	+23
95% CI (change vs placebo)		(-33, 27)	(-15, 45)
P-value (ANOVA\)		0.851	0.314

Change in 6MWD by Treatment and by LTOT Use

LTOT group	Placebo	25 iNO	75 iNO
N analyzed	10	15	18
Baseline (meters, mean)	334	302	292
Change from baseline (mean)	-11	+9	+35
95% CI (change vs placebo)		(10, 59)	(7, 84)
Non- LTOT group			
N analyzed	14	9	5
Baseline (meters, mean)	397	364	331
Change from baseline (mean)	+20	-3	-21
95% CI (change vs placebo)		(-70, 23)	(-98, 15)

Device Compliance was Highly Variable and Better in Subjects on LTOT



Conclusions

- The present study is the first to assess in a randomized double-blind placebo controlled manner the ambulatory administration of NO in PAH. Limitations of this phase 2 study include the small size of the study, and the inter-subject variability of study drug administration.
- In the ITT population, iNO did not significantly affect the PVR or 6MWD in patients with PAH
- Safety of iNO appeared acceptable
- For patient subjects who received supplemental oxygen at baseline, the 6MWD increased from baseline in the two iNO cohorts and decreased in the placebo cohort. A statistically significant difference was observed between the iNO 75 mcg cohort and the placebo cohort in the mean change from baseline in the 6MWD ($p = 0.021$). A smaller treatment difference, which was not statistically significant, was observed between the iNO 25 mcg cohort and the placebo cohort.
- Exploratory analyses suggest settings where increased adherence, such as use in LTOT, could be a way forward in future studies of iNO in PAH