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): 12 month interim analysis of open label extension

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Abstract

Rationale: iNO is a selective pulmonary vasodilator. Clinical experience suggests iNO has the potential to treat PAH.

Methods: A Phase 2 placebo-controlled trial of two doses of iNO in PAH patients on at least one background PAH therapy was completed. After 16 weeks of blinded treatment (Part 1, n=80), patients entered the long-term extension phase (Part 2). In Part 2 the patients originally receiving iNO 75 mcg/kg (IBW/hr) or iNO 25 mcg/kg (IBW/hr) remained on their assigned treatment, while patients from the placebo group were randomized (double-blind) to either iNO 75 or 25 mcg/kg. Eleven patients randomized to iNO and 4 patients randomized to placebo in Part 1 did not enter Part 2. In Part 2, the primary endpoint was pulmonary vascular resistance (PVR), and a key secondary endpoint was a six minute walk distance (6 MWD), both assessed as the change from the time of randomization to 25 mcg/kg or 75 mcg/kg iNO to 12 months. The primary analysis included all patients randomly assigned to 25 or 75 mcg/kg iNO (N=76), while exploratory analyses included an assessment by subgroups on (LTOT) and not on (non LTOT) long-term oxygen therapy.

Results: In the year following randomization to iNO treatment, 28 of 76 patients discontinued iNO without evaluation of PVR and 3 patients died. Twelve months after randomization, 6 of 37 (16%) patients who received iNO 25 mcg/kg and 9 of 39 (23%) patients who received iNO 75 mcg/kg had ≥ 20% reduction in PVR (Table 1), while 6 of 37 (16%) patients who received iNO 25 mcg/kg and 10 of 39 (26%) patients who received iNO 75 mcg/kg had ≥ 50 meter increase in 6MWD (Table 2). The tables suggest efficacy may differ according to LTOT status.

In patients with ≤ 32 months of exposure, serious adverse events (SAE) occurred in 5/32 in the 25 mcg/kg group and 12/33 in the 75 mcg/kg groups. Unexpectedly, drug-related SAEs occurred in 6 and 0 patients, respectively.

Conclusion: In this small Phase II trial without a long term control regimen, even though caution is needed when considering signals of efficacy especially in exploratory subgroup analyses, the data suggests interest in further evaluation of the 75 mcg/kg group, potentially focusing on subjects on LTOT where adherence may be enhanced. The sponsor plans a phase III trial.

Background

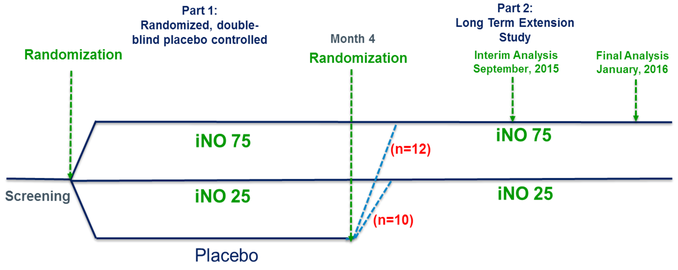
iNO is a selective pulmonary vasodilator. The mechanism of NO-mediated vasodilation occurs via the activation of soluble guanylate cyclase, the production of cyclic guanosine monophosphate, and subsequent relaxation of vascular smooth muscle. iNO produces pulmonary vasodilation with minimal effect on 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

INOpulse for PAH: Phase II Trial

- **Part 1 – 16 weeks of blinded therapy**
  - **Evaluate effect of iNO on hemodynamic measures and 6MWD in ambulatory PAH patients on at least one approved therapy**
  - **Patients randomized to iNO 25, iNO 75 or Placebo**
  - **66 subjects completed Part 1**
- **Part 2 – Long Term Extension Study**
  - **Placebo patients randomized to receive either iNO 25 or iNO 75**
  - **65 subjects entered Part 2**
  - **During Part 2: 4 additional subjects were treated with LTOT**



Results:

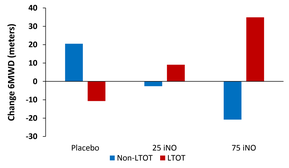
6MWD and PVR Results from Part 1: 16 weeks

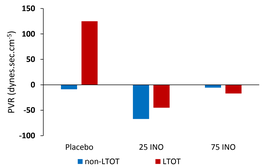
6MWD: Change vs. Baseline (Mean)

	N	Placebo	25 iNO	75 iNO
Non-LTOT	38	20.5	-2.6	-20.8
LTOT	**43**	-10.7	9.1	**34.9***

Resting PVR: Change vs. Baseline (Mean)

	N	Placebo	25 iNO	75 iNO
Non-LTOT	37	-8.7	-67.1	-5.6
LTOT	**44**	+125.5	-47.1*	**-17.5**





Units for PVR: dynes sec.cm^{-5}; Units for 6MWD: meters

*** p<0.05 vs. placebo**

Results: PART 2

Table 1. Changes in PVR from Randomization to Month 12

	Overall Trial		LTOT		Non-LTOT	
Randomized iNO mcg/kg	25	75	25	75	25	75
At least 20% Reduction	6(16%)	9(23%)	4(19%)	7(29%)	2(12%)	2(13%)
0 to 20% Reduction	9(24%)	6(15%)	6(29%)	3(12%)	3(19%)	3(20%)
Increase	4	8	3	4	1	4
Discont Rx w/o Eval	17	11	7	6	10	5
Confirmed Death	1	2	1	1	0	1
* Missing PVR	0	3	0	3	0	0
Total	37	39	21	24	16	15

* Had 12 month visit, yet PVR assessment not made.

Table 2. Changes in 6MWD from Randomization to Month 12

	Overall Trial		LTOT		Non-LTOT	
Randomized iNO mcg/kg	25	75	25	75	25	75
At least 50 meter increase	6(16%)	10(26%)	4(19%)	9(37%)	2(12%)	1(7%)
0 to 50 meter increase	4(11%)	8(21%)	4(19%)	5(21%)	0(0%)	3(20%)
Decrease	9	8	5	3	4	5
Discont Rx w/o Eval	17	11	7	6	10	5
Confirmed Death	1	2	1	1	0	1
Total	37	39	21	24	16	15

INOpulse device used in PARTs 1 and 2 of this Phase II Clinical Trial

New INOpulse device for iNO Phase III Clinical Trial

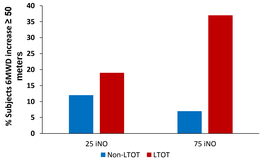
6MWD and PVR Results from Part 2: 12 months

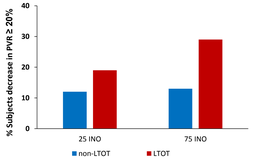
6MWD: % Subjects with increase in 6MWD ≥ 50 meters

	N	25 iNO	75 iNO
Non-LTOT	3	12%	7%
LTOT	**13**	19%	**37%**

Resting PVR: % Subjects with PVR reduction ≥ 20%

	N	25 iNO	75 iNO
Non-LTOT	4	12%	13%
LTOT	**11**	19%	**29%**





Units for PVR: dynes sec.cm^{-5}; Units for 6MWD: meters

Safety Results

Treatment Emergent Adverse Events Occurring in More Than 10% of Subjects in Any Dose Cohort During Part 1 or Part 2 by System Organ Class and Preferred Term (Safety Population)

201 – PART 1

System Organ Class	Placebo N=26 n (%)	0.025 mg/kg IBW/hr N=27 n (%)	0.075 mg/kg IBW/hr N=27 n (%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
Epistaxis	7 (26.9)	7 (25.9)	7 (25.9)
Dyspnea	2 (7.7)	6 (22.2)	6 (22.2)
Cough	0 (0.0)	2 (7.4)	2 (7.4)
Nasal congestion	2 (7.7)	1 (3.7)	4 (14.8)
Hypoxia	0 (0.0)	0 (0.0)	3 (11.1)
Nasal mucosal disorder	1(3.7)	1 (3.7)	2 (7.4)
INFECTIONS AND INFESTATIONS			
Nasopharyngitis	2 (7.7)	1 (3.7)	3 (11.1)
Upper respiratory tract infection	3 (11.5)	1 (3.7)	2 (7.4)
Bronchitis	0 (0.0)	1 (3.7)	4 (14.8)
Pneumonia	1(3.8)	2 (7.4)	1 (3.7)
Device related infection	2 (7.7)	0 (0.0)	0 (0.0)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
Edema peripheral	0 (0.0)	2 (7.4)	3 (11.1)
Chest pain	2 (7.7)	2 (7.4)	1 (3.7)
METABOLISM AND NUTRITION DISORDERS			
Hypokalaemia	3 (11.5)	4 (14.8)	1 (3.7)
Gout	1 (3.8)	1 (3.7)	3 (11.1)
MUSCULOSKELETAL AND CONNECTIVE TISSUES DISORDERS			
Pain in extremity	0 (0.0)	3 (11.1)	0 (0.0)

201 – PART 2

0.025 mg/kg IBW/hr N=32 n (%)	0.075 mg/kg IBW/hr N=33 n (%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	
8 (25.0)	10 (30.3)
3 (9.4)	4 (12.1)
4 (12.5)	2 (6.1)
1 (3.1)	5 (15.2)
0 (0.0)	3 (11.1)
4 (12.5)	2 (6.1)
INFECTIONS AND INFESTATIONS	
0 (0.0)	0 (0.0)
4 (12.5)	2 (6.1)
1 (3.1)	5 (15.2)
2 (6.3)	5 (15.2)
4 (12.5)	0 (0.0)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	
3 (9.4)	4 (12.1)
2 (6.3)	4 (12.1)
METABOLISM AND NUTRITION DISORDERS	
4 (12.5)	3 (9.1)
0 (0.0)	0 (0.0)
MUSCULOSKELETAL CONNECTIVE TISSUE DISORDERS	
0 (0.0)	0 (0.0)

Note: Multiple occurrences of an event in a subject are counted once. Incidence rates are sorted by highest SOC frequency and then highest PT frequency within SOC.
IBW = ideal body weight; PT = preferred term; SOC = system organ class

Cohort 1: P-25 (N = 10)
Cohort 2: P-75 (N = 12)
Cohort 3: 25-25 (N = 22)
Cohort 4: 75-75 (N = 21)

In patients with ≤ 32 months of exposure, serious adverse events (SAE) occurred in 5/32 in the 25 mcg/kg group and 12/33 in the 75 mcg/kg groups. Unexpectedly, drug-related SAEs occurred in 6 and 0 patients, respectively.

Conclusion

Conclusion: In this small Phase II trial without a long term control regimen, even though caution is needed when considering signals of efficacy especially in exploratory subgroup analyses, the data suggest interest in further evaluation of the 75 mcg/kg group, potentially focusing on subjects on LTOT where adherence may be enhanced. Safety results from patient subjects in this small Phase II study did not identify any specific safety signal. Bellerophon Therapeutics is currently conducting a Phase III study with a smaller iNO delivery device.