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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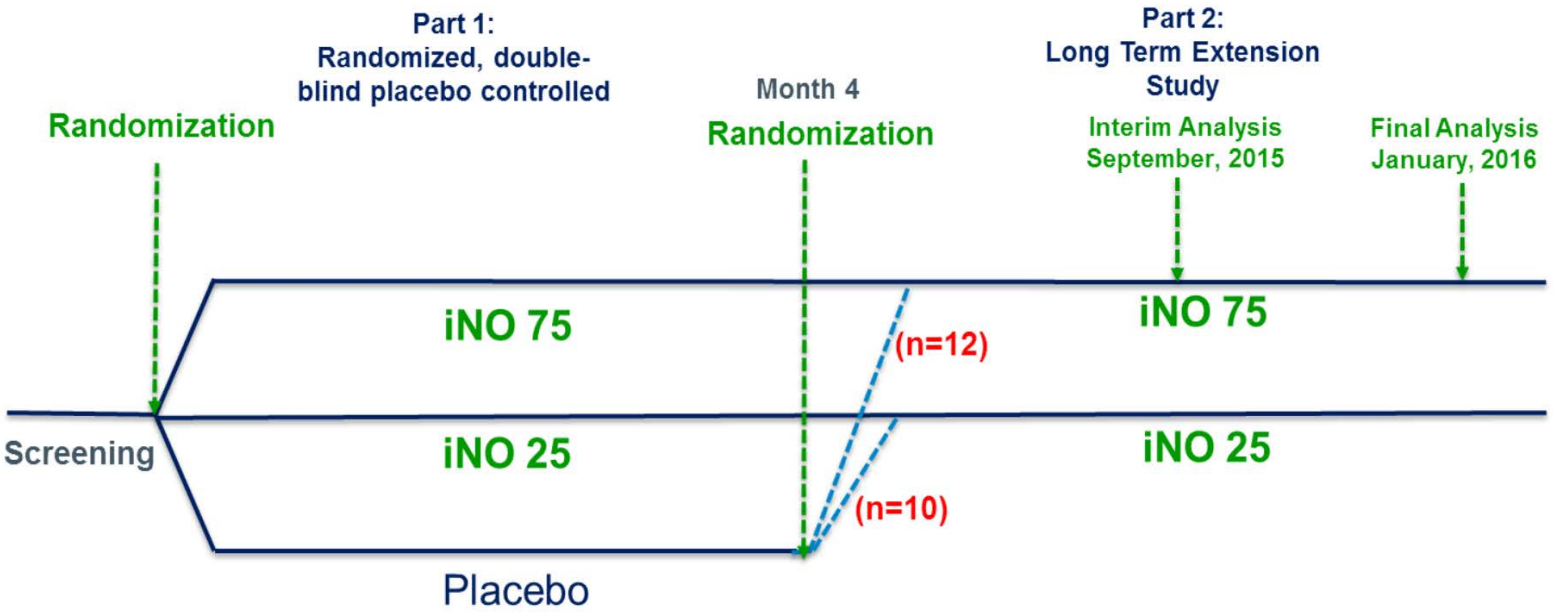
INOPULSE for PAH Phase 2 (Part 2)

- 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
  - 80 enrolled; 71 evaluable; 66 completed
- **Part 2 – Long Term Extension Clinical Trial**
  - **Patients who completed Part 1 offered extension into long term clinical trial with 65 of 66 choosing to continue treatment**
  - **Placebo patients randomized to receive either iNO 25 or iNO 75**

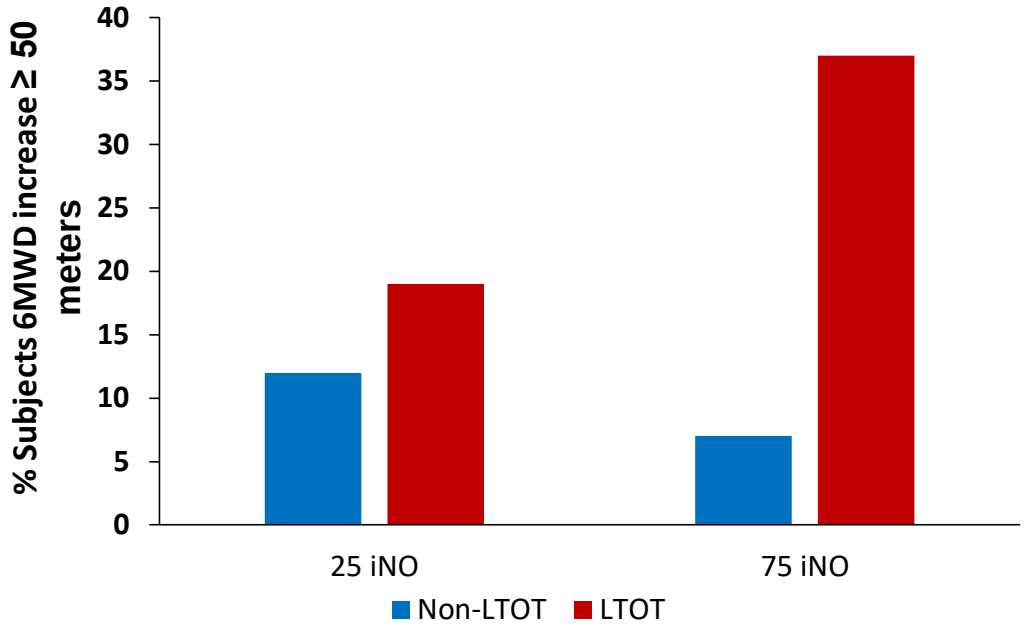


Phase 2 INOPULSE Device

Results: PAH Phase 2- Part 2: 6MWD and PVR

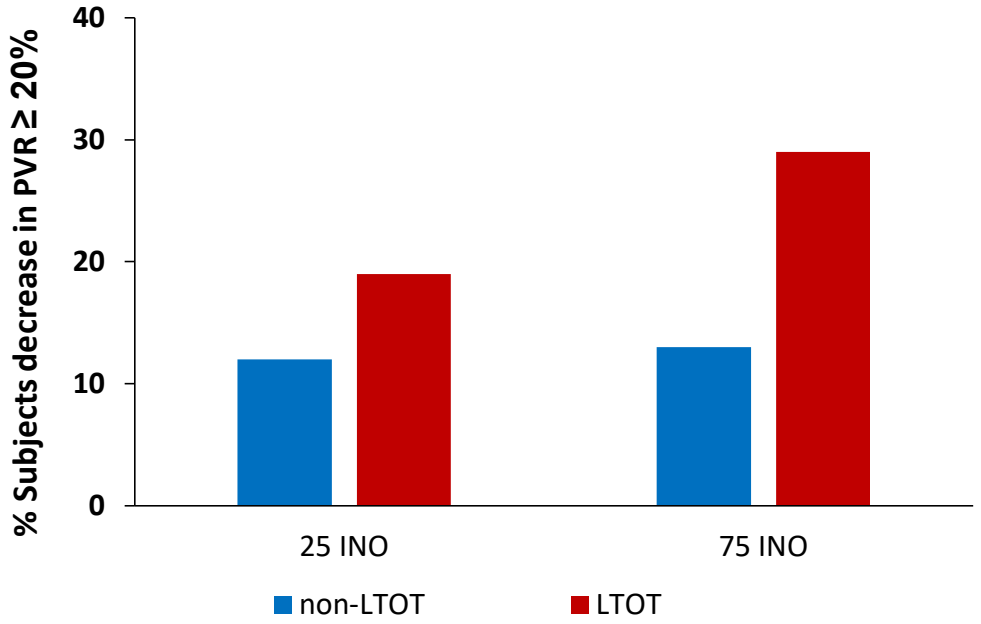
6MWD: % Subjects with increase in 6MWD ≥ 50 meters

	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%**

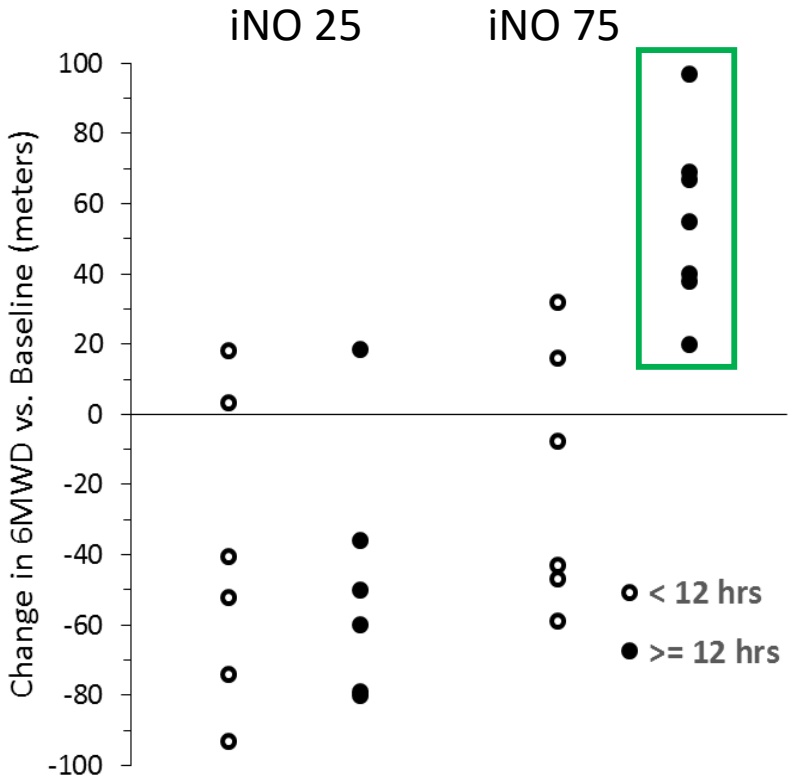


Units for PVR: dynes sec.cm^{-5}; Units for 6MWD: meters

Results: PAH Phase 2 – Part 2 (Long-Term Extension) Data Current Durability of Effect

- After 16-32 months of treatment patients on iNO 75 who remained on therapy for ≥ 12 hrs/day in combination with LTOT maintained a consistent and clinically significant increase in 6MWD
- All subjects have now been transitioned to Long-Term Open Label iNO 75

	iNO 25		iNO 75	
Δ6MWD (meters)	Mean	N	Mean	N
All LTOT	-43.7	12	21.4	13
iNO 75 <12 hrs plus LTOT	-39.7	6	-18.0	6
iNO 75 ≥12 hrs plus LTOT	-47.7	6	55.2	7



Results: PAH Phase 2-Part 2 iNO

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

Safety Results: PAH Phase 2-Part 2

- 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

- **No significant safety issues or trends** were observed in our Phase 2 Study including the Part 2 Open Label Extension of this study

- **Overall Safety Summary:**
  - 52% of subjects have had no SAEs reported
  - No SAEs reported as “probably related” to study drug or device
  - Only 2 SAEs reported as “possibly related” to study drug or device and both subjects continued on iNO
  - All other SAEs have been reported as “unrelated” to study drug or device

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)

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

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)	0 (0.0))
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)

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

PAH PHASE 2 Results Informed Current PHASE 3 Program

Phase 3 smaller INOPULSE Device

FDA has agreed (January 2017) to an accelerated clinical program

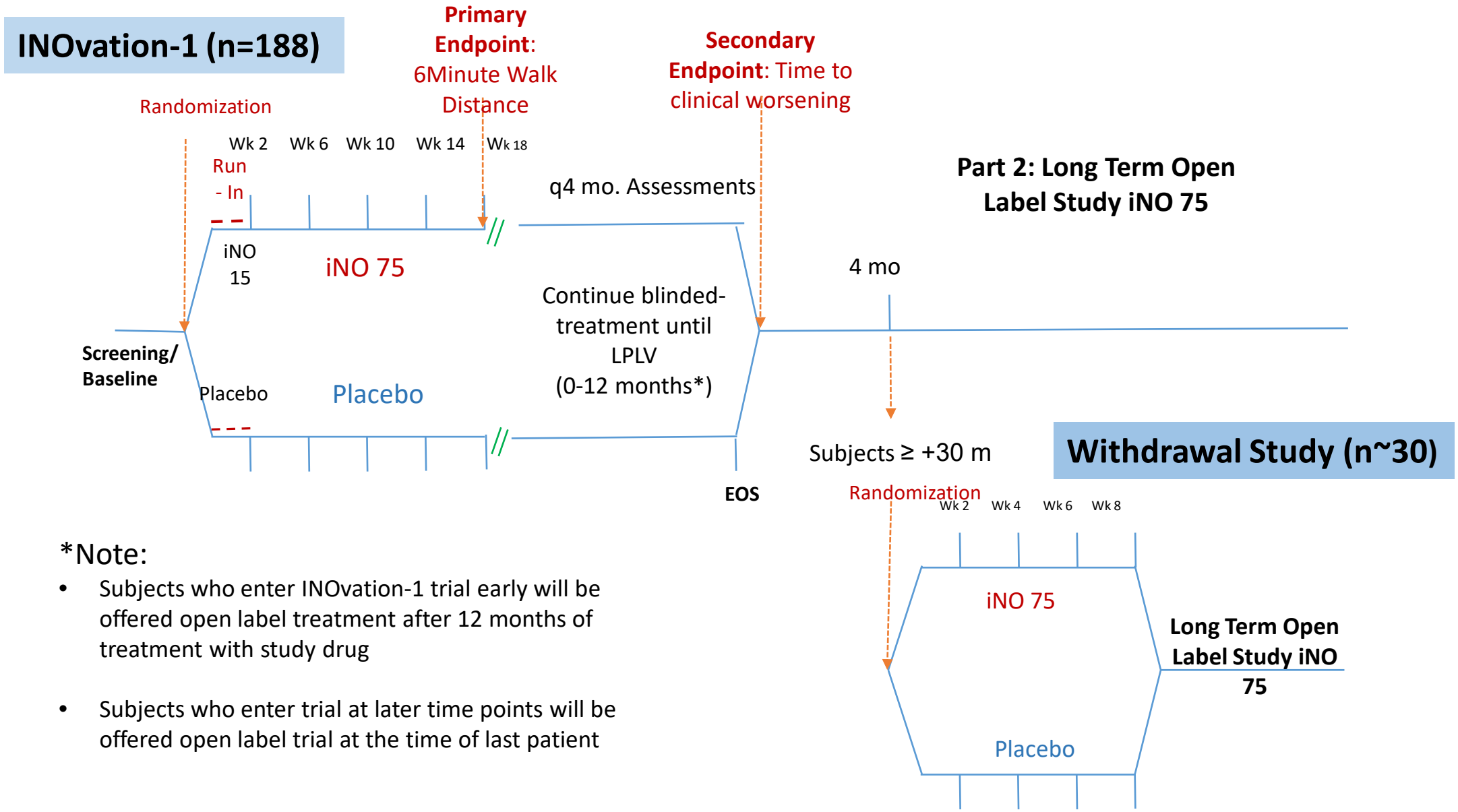
- **1st Phase 3 Study (initiated in June 2016) INOvation-1**
  - 2 arms (iNO 75 and Placebo) with 94 subjects on LTOT per arm
  - Primary Endpoint: improvement in 6MWD compared to placebo after 16 weeks

- **2nd Phase 3 Study (planned start in 2H 2017)**

A Randomized Placebo Controlled Withdrawal Study in an Enriched Population of Pulmonary Arterial Hypertension Patient Subjects with Long Term Oxygen Use that have Demonstrated Improved Exercise Tolerance with the Use of Inhaled Nitric Oxide

- 2 arms (iNO 75 and Placebo) with ~20 subjects per arm rolled over from 1st Phase 3 study
- Primary Endpoint: increase in TTCW when compared to placebo during 8 week withdrawal phase

PHASE III Program



*Note:

- Subjects who enter INOvation-1 trial early will be offered open label treatment after 12 months of treatment with study drug
- Subjects who enter trial at later time points will be offered open label trial at the time of last patient

Timelines to NDA Submission: iNO
Decrease time to approval and access to patients