APPENDIX 1

TITLE:	**Comparison of Supplemental Oxygen and Nitric Oxide for Inhalation Plus Oxygen in the Evaluation of the Reactivity of the Pulmonary Vasculature During Acute Pulmonary Vasodilator Testing**
DRUG:	INOmax® (nitric oxide) for inhalation
INDICATION:	Diagnostic Use
SPONSOR:	INO Therapeutics 6 Route 173 Clinton, NJ 08809
PROTOCOL:	INOT22
DRUG DEVELOPMENT PHASE:	Phase 3
VERSION:	Amendment 1
DOCUMENT DATE:	[redacted]
STUDY INITIATION:	
STUDY DURATION:	1½ years
MEDICAL MONITOR:	James S. Baldassarre, MD Senior Director of Research & Development Phone (908) 238-6363 Fax (908) 238-6634
REGULATORY CONTACT:	Mary Ellen Zamstein U.S. & Canadian Regulatory Affairs
STUDY CONTACT:	Jodee Newman Project Leader Phone (908) 238-6317 Fax (908) 238-6634
GCP:	These studies will be performed in compliance with good clinical practices (GCP) guidelines. All essential documents will be archived.

2. SYNOPSIS

Sponsor: INO Therapeutics, LLC	
Name of Finished Product: INOmax® (nitric oxide) for inhalation	
Name of Active Ingredient: Nitric Oxide for Inhalation	
Protocol Number: INOT22	
Title of Study: Comparison of Supplemental Oxygen and Nitric Oxide for Inhalation Plus Oxygen in the Evaluation of the Reactivity of the Pulmonary Vasculature During Acute Pulmonary Vasodilator Testing	
Investigators: Pr. Daniel Sidi, Dr. Alain Fraisse, Dr. Federico Larraya, Dr. Jose Luis Zunzunegui, Dr. Joaquin Jose Bartrons, Prof. Dr. Rolf Berger, Dr. Alan Magee, Dr. Mary Mullen, Dr. Robyn Barst	
Study Centers: Hopital Necker, Paris, France; CHU la Timone-Hopital d'enfants, Marseille, France; Hospital Materno-Infantil XII de Octubre, Madrid, Spain; Hospital Gregorio Maranon, Madrid Spain; Hospital Sant Joan de Deu, Barcelona, Spain; Beatrix Children's Hospital, Univ. Hospital Groningen, Amsterdam, Netherlands; The Royal Brompton Hospital, London, UK; Boston Children's Hospital, Boston, MA, US; Columbia Presbyterian Hosptital, New York, NY, US.	
Study Period: [redacted]	**Phase of development:** III
Objectives: Compare utility and side effects of oxygen versus nitric oxide for inhalation plus oxygen in determining pulmonary vasoreactivity.	
Methodology: An open, prospective, randomized, multi-center, controlled diagnostic trial.	

Number of patients planned: Enrollment will proceed until at least 25 patients per entry diagnosis and at least 150 patients have been enrolled.
Anticipated duration of trial: 1½ years

[redacted]

Diagnosis and main criteria for inclusion: Patients between the ages of 4 weeks and eighteen years undergoing diagnostic right heart catheterization scheduled to include acute pulmonary vasodilation testing to assess pulmonary vasoreactivity. The expected population will be patients with: 1) Idiopathic Pulmonary Arterial Hypertension 2) Congenital heart disease with pulmonary hypertension; 3) Cardiomyopathies; Patients who are either under general anesthesia or awake sedation will be included in this protocol. Patients will be stratified based on entry diagnosis.
Test product, dose and mode of administration: Nitric oxide for inhalation 800 ppm, administered at a dose of 80 ppm, nitric oxide for inhalation plus 100% O_2 and 100% O_2; via facemask or endotracheal tube.
Duration of treatment: 10 minutes of nitric oxide for inhalation at 80 ppm and 10 minutes of 80 ppm nitric oxide for inhalation plus 100% O_2, and 10 minutes of 100% O_2; delivered via facemask or endotracheal tube.

Criteria for evaluation:

Primary endpoint:

Number of patients receiving a combination of NO and O_2 versus the number of patients receiving O_2 alone that meet response criteria. The response criteria are as follows:

Patients with Idiopathic Pulmonary Arterial Hypertension or patients with CHD who do not have an unrestricted shunt at the level of the ventricle or ductus arteriosus, response will be defined as:

1) a decrease in PAPm ≥ 20% and no decrease in cardiac index (within 5%)

Patients with cardiomyopathy or patients with CHD who have an unrestricted shunt at the level of the ventricle or ductus arteriosus, response will be defined as:

1) a decrease in PAPm ≥ 20% and no decrease in cardiac index (within 5%)

or

2) a decrease in PVRI ≥ 25% and no decrease in cardiac index (within 5%)

Secondary endpoints:

1) Number of patients receiving NO versus the number of patients receiving O_2 that meet response criteria, as defined above.
2) Number of patients receiving a combination of NO and O_2 versus the number of patients receiving NO alone that meet response criteria, as defined above.
3) PVRI, PAPm and Cardiac Index readings in Room Air versus NO alone, O_2 alone and the combination of NO and O_2
4) Change in the ratio of PAPm to SAPm by treatment
5) Survival at 1 year by response

Safety endpoints:

1) Incidence and types of reported serious adverse events.
2) Incidence and types of drug related adverse events.

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