

APPENDIX 3

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 II

DOCUMENT DATE: [REDACTED]

STUDY INITIATION: [REDACTED]

STUDY DURATION: 2 years

MEDICAL MONITOR: James S. Baldassarre, MD
Senior Director of Research & Development
Phone (908) 238-6363
Fax (908) 238-6634

REGULATORY CONTACT: Sandra Cottrell
VP-Global Regulatory Affairs

Mary Ellen Zamstein
U.S. & Canadian Regulatory Affairs

STUDY CONTACT: Jodee Newman, RN
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.

Version: Amendment II



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, et al. TBD	
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 Hospital, New York, NY, US, et al. TBD	
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: 2 years	

Version: Amendment II



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% O₂ and 100% O₂, 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% O₂, and 10 minutes of 100% O₂; delivered via facemask or endotracheal tube.

Criteria for evaluation:

Primary endpoint:

Number of patients receiving a combination of NO and O₂ versus the number of patients receiving O₂ 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 \geq 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 \geq 20% and no decrease in cardiac index (within 5%)

or

- 2) a decrease in PVRI \geq 25% and no decrease in cardiac index (within 5%)

Secondary endpoints:

- 1) Number of patients receiving NO versus the number of patients receiving O₂ that meet response criteria, as defined above.
- 2) Number of patients receiving a combination of NO and O₂ 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, O₂ alone and the combination of NO and O₂
- 4) Change in the ratio of PAPm to SAPm by treatment
- 5) Survival at 1 year and 3 years by response

Safety endpoints:

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



3. TABLE OF CONTENTS

- 1. TITLE PAGE**
- 2. SYNOPSIS..... 1**
- 3. TABLE OF CONTENTS 4**
- 4. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS..... 6**
- 5. ETHICS 11**
 - 5.1 INSTITUTIONAL REVIEW BOARD (IRB) / INDEPENDENT ETHICS COMMITTEE (IEC) 11
 - 5.2 ETHICAL CONDUCT OF THE STUDY 11
 - 5.3 PATIENT INFORMATION AND INFORMED CONSENT 11
 - 5.4 FINANCIAL INTEREST STATEMENT..... 12
- 6. INVESTIGATORS AND STUDY ADMINISTRATION STRUCTURE..... 13**
 - 6.1 INVESTIGATORS 13
 - 6.2 ADMINISTRATIVE STRUCTURE 13
 - 6.3 STEERING COMMITTEE MEMBERS..... 13
 - 6.4 DATA SAFETY AND MONITORING BOARD MEMBERS 13
- 7. INTRODUCTION..... 15**
- 8. STUDY OBJECTIVES..... 17**
- 9. INVESTIGATIONAL PLAN 18**
 - 9.1 OVERALL STUDY PLAN AND DESIGN 18
 - 9.2 DISCUSSION OF STUDY DESIGN..... 19
 - 9.3 SELECTION OF STUDY POPULATION 19
 - 9.3.1 Inclusion Criteria..... 19
 - 9.3.2 Exclusion Criteria..... 20
 - 9.3.3 Removal of Patients from Therapy or Assessment..... 20
 - 9.4 TREATMENTS 21
 - 9.4.1 Treatments Administered..... 21
 - 9.4.2 Identity of Investigational Product 21
 - 9.4.3 Method of Assigning Patients to Treatment Groups..... 22
 - 9.4.4 Selection of Doses in the Study..... 22
 - 9.4.5 Selection and Timing of Dose for Each Patient..... 22
 - 9.4.6 Treatment Group Assignment Blinding 22
 - 9.4.7 Prior and Concomitant Therapy..... 23
 - 9.4.8 Treatment Compliance..... 23
 - 9.5 EFFICACY AND SAFETY VARIABLES..... 24
 - 9.5.1 Efficacy and Safety Schedule of Assessments 24
 - 9.5.2 Data Collection..... 25
 - 9.5.3 Ventilator Weaning and Extubation Strategy 31
 - 9.5.4 Appropriateness of Measurements..... 31
 - 9.5.5 Efficacy Variables..... 32
 - 9.5.6 Safety Variables..... 33

Version: Amendment II



Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts



Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research



With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips



Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS

Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS

Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS

Sync your system to PACER to automate legal marketing.