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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/454,373	08/07/2014	James S. Baldassarre	26047-0003011	3860

94169 7590 12/01/2015

Fish & Richardson PC
P.O.Box 1022
minneapolis, MN 55440

EXAMINER	
ARNOLD, ERNST V	

ART UNIT	PAPER NUMBER
1613	

MAIL DATE	DELIVERY MODE
12/01/2015	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of Abandonment	Application No.	Applicant(s)
	14/454,373	BALDASSARRE, JAMES S.
	Examiner	Art Unit
	ERNST V. ARNOLD	1613

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

This application is abandoned in view of:

1. ☒ Applicant's failure to timely file a proper reply to the Office letter mailed on *29 April 2015*.
   (a) ☐ A reply was received on _____ (with a Certificate of Mailing or Transmission dated _____), which is after the expiration of the period for reply (including a total extension of time of _____ month(s)) which expired on _____.
   (b) ☐ A proposed reply was received on _____, but it does not constitute a proper reply under 37 CFR 1.113 to the final rejection.
   (A proper reply under 37 CFR 1.113 to a final rejection consists only of: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) if this is utility or plant application, a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. Note that RCEs are not permitted in design applications.)
   (c) ☐ A reply was received on _____ but it does not constitute a proper reply, or a bona fide attempt at a proper reply, to the non-final rejection. See 37 CFR 1.85(a) and 1.111. (See explanation in box 7 below).
   (d) ☒ No reply has been received.

2. ☐ Applicant's failure to timely pay the required issue fee and publication fee, if applicable, within the statutory period of three months from the mailing date of the Notice of Allowance (PTOL-85).
   (a) ☐ The issue fee and publication fee, if applicable, was received on _____ (with a Certificate of Mailing or Transmission dated _____), which is after the expiration of the statutory period for payment of the issue fee (and publication fee) set in the Notice of Allowance (PTOL-85).
   (b) ☐ The submitted fee of $_____ is insufficient. A balance of $_____ is due.
   The issue fee required by 37 CFR 1.18 is $_____. The publication fee, if required by 37 CFR 1.18(d), is $_____.
   (c) ☐ The issue fee and publication fee, if applicable, has not been received.

3. ☐ Applicant's failure to timely file corrected drawings as required by, and within the three-month period set in, the Notice of Allowability (PTO-37).
   (a) ☐ Proposed corrected drawings were received on _____ (with a Certificate of Mailing or Transmission dated _____), which is after the expiration of the period for reply.
   (b) ☐ No corrected drawings have been received.

4. ☐ The letter of express abandonment which is signed by the attorney or agent of record or other party authorized under 37 CFR 1.33(b). See 37 CFR 1.138(b).

5. ☐ The letter of express abandonment which is signed by an attorney or agent (acting in a representative capacity under 37 CFR 1.34) upon the filing of a continuing application.

6. ☐ The decision by the Board of Patent Appeals and Interference rendered on _____ and because the period for seeking court review of the decision has expired and there are no allowed claims.

7. ☒ The reason(s) below:

The six month statutory period of reply expired on 10/29/15 with no reply from Applicant.

/ERNST V ARNOLD/
Primary Examiner, Art Unit 1613

Petitions to revive under 37 CFR 1.137, or requests to withdraw the holding of abandonment under 37 CFR 1.181, should be promptly filed to minimize any negative effects on patent term.

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EXAMINER
ARNOLD, ERNST V

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1613	

MAIL DATE	DELIVERY MODE
04/29/2015	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 14/454,373	Applicant(s) BALDASSARRE, JAMES S.	
	Examiner ERNST V. ARNOLD	Art Unit 1613	AIA (First Inventor to File) Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *2/6/15*.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5)☒ Claim(s) *31-60* is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *31-60* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)

2) ☒ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date *2/6/15*.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

4) ☐ Other: _____.

The present application is being examined under the pre-AIA first to invent provisions.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after allowance or after an Office action under *Ex Parte Quayle*, 25 USPQ 74, 453 O.G. 213 (Comm'r Pat. 1935). Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on 2/6/15 has been entered.

Claims 31-60 are pending and under examination.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on 2/6/15 was filed after the mailing date of the NOA on 11/20/14. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Claim Rejections - 35 USC § 112

The following is a quotation of 35 U.S.C. 112(b):

(b) CONCLUSION.—The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the inventor or a joint inventor regards as the invention.

The following is a quotation of 35 U.S.C. 112 (pre-AIA), second paragraph:
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 54-60 are rejected under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the inventor or a joint inventor, or for pre-AIA the applicant regards as the invention. Claim 54 is directed to steps (a-d) where steps (b-d) are:

(b) determining that, because the patient has pre-existing left ventricular dysfunction, the patient is at particular risk of pulmonary edema when treated with inhaled nitric oxide;
(c) treating the patient with 20 ppm inhaled nitric oxide; and
(d) discontinuing the inhaled nitric oxide treatment due to the determination of (b).

It is unclear to the Examiner how step (c) can be performed at all when (d) requires cessation of iNO treatment due to determination of step (b) which comes before step (c). One knows (b) before performing (c). This is a self-referential paradox of performing steps that contradict one another. While the claim is directed to reducing the risk of inducing pulmonary edema and has the artisan determining that the patient has pre-existing LVD and is at risk of pulmonary edema when treated with iNO, the claim also then has the artisan treat the patient with iNO. Then the artisan remembers that iNO can cause pulmonary edema in this situation and so discontinues the iNO treatment. This makes no sense. The claim preamble states that the method ***reduces the risk*** of inducing pulmonary edema and step (b) states that patients with pre-existing LVD are at particular risk of pulmonary edema when treated with iNO. The artisan would not then

treat the patient with iNO which would ***increase the risk*** of inducing pulmonary edema. That is contradictory to the purpose of the method. The discontinuation is due to determination of pre-existing LVD and therefore once pre-existing LVD is determined in step (b), step (c) would not be performed as that would increase the risk of inducing pulmonary edema. Therefore, the claimed subject matter is paradoxical and indefinite.

Dependent claims are rejected as indefinite because they are dependent upon an indefinite base claim. These claims cannot be further examined as it would be speculation as to what method steps are intended to be claimed. MPEP 2173.06 II: "…where there is a great deal of confusion and uncertainty as to the proper interpretation of the limitations of a claim, it would not be proper to reject such a claim on the basis of prior art. As stated in *In re Steele*, 305 F.2d 859, 134 USPQ 292 (CCPA 1962), a rejection under 35 U.S.C. 103 should not be based on considerable speculation about the meaning of terms employed in a claim or assumptions that must be made as to the scope of the claims."

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 31-53 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zapol (US 5570683) and Bland (Acta Paediatr Scand. 1983, Suppl 305:92-99) and Jaypee (Pediatric and Neonatal Mechanical Ventilation 2006, Jaypee Brothers Publishers, Khilnani pages 155-156) and Greenough (Neonatal Respiratory Disorders 2003, 2ed; CRC Press: pages 183-187 and 392) and Wyka et al. (Foundations of Respiratory Care, Cengage Learning, 2002:pages 503-504) and Marter (chapter in: Cloherty et al. Manual of Neonatal Care, 2004, 5th edition, pages 377-382 (IDS filed 2/6/15).

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Applicant claims for example:

> 31. (New) A method of improving the safety of treating hypoxic respiratory failure in neonates by reducing the risk of inducing pulmonary edema, the method comprising:
>
> (a) identifying a plurality of neonatal patients who have hypoxic respiratory failure;
>
> (b) determining that a first patient of the plurality does not have pre-existing left ventricular dysfunction;
>
> (c) administering a first treatment regimen to the first patient, wherein the first treatment regimen comprises administration of 20 ppm inhaled nitric oxide for 14 days or until the first patient's hypoxia has resolved;
>
> (d) determining that a second patient of the plurality has pre-existing left ventricular dysfunction, so is at particular risk of pulmonary edema upon treatment with inhaled nitric oxide; and
>
> (e) based on the determination of (d), selecting and administering a second treatment regimen to the second patient, wherein the second treatment regimen does not comprise either (i) administration of inhaled nitric oxide for 14 days or (ii) administration of inhaled nitric oxide until the second patient's hypoxia has resolved, and does comprise one or more other therapies selected from vasodilators, intravenous fluids, bicarbonate therapy and mechanical ventilation.

Determination of the scope and content of the prior art

(MPEP 2141.01)

Zapol teaches methods of identifying patients for whom an improvement in gas exchange in the lung would be beneficial and providing NO gas to the hypoxic mammal for inhalation (claims 26 and 27). Zapol teach treating patients, such as humans, that have or are at risk of developing clinical conditions such as persistent pulmonary hypertension of the newborn, hence term or near-term neonates, hypoxia and chronic hypoxia (column 4, lines 51-column 5, line 1; and claims 3, 4 and 15) by administration of inhaled NO gas at a concentration of at least 0.01 ppm (claims 1 and 7-9). To know the patient population, it is implicit that the patient was diagnosed with the condition. Zapol warns that when the capillary wedge pressure increases pulmonary edema can

result that can be fatal (column 2, lines 7-30). Indeed, Zapol suggests various direct and indirect monitoring methods such as ultrasound and Doppler techniques (echocardiography) to measure the pulmonary artery pressure (column 12, lines 56-67). Zapol also warns that higher levels of NO can produce NO_2 which can produce ***pulmonary edema*** (column 3, lines 40-44). Zapol teaches that the invention produces pulmonary vasodilation and increased blood flow to the alveoli (Examiner added emphasis): "…*an important advantage of both the bronchodilating and the pulmonary vasodilating methods of the invention is that one can selectively prevent or treat bronchospasm and/or pulmonary hypertension without producing a concomitant lowering of the systemic blood pressure to potentially dangerous levels. The invention allows for effective reversal of pulmonary hypertension without the risk of underperfusion of vital organs, venous pooling, ischemia, and heart failure that may accompany systemic vasodilation. Such isolated pulmonary vasodilation is also important in treating PPHN in newborn infants, as systemic vasodilation aggravates the undesired mixing of oxygenated and de-oxygenated blood through the ductus arteriosus or the foramen ovale of newborns. Furthermore, by concomitantly bronchodilating and* ***increasing blood flow to ventilated alveoli***,…" (column 9, line 67-column 10, line 13). It is important to note the increased blood flow to the alveoli.

Zapol suggest administration of 0.001 ppm to 40 ppm NO in air, pure oxygen or other suitable gas (column 12, lines 45-48) and teaches that 20 ppm increases blood oxygen levels in human patients (column 13, lines 5-12).

Bland teaches premature newborn infants are at increased risk of acquiring pulmonary edema (page 98, Implications) and that neonatal pulmonary edema often results from sustained hypoxia, in left ventricular failure associated with congenital heart disease and in conditions that increase pulmonary blood flow (Abstract). Thus, measures that may lessen the likelihood of edema formation or reduce its severity are to avoid conditions that increase blood flow to the lungs (bottom right page 98 through top left page 99). Bland also teaches that edema often accompanies interstitial emphysema where water can accumulate in the lungs (Abstract and page 97, lower left column). Indeed, pulmonary interstitial emphysema is a condition that may interfere with lymphatic drainage in the newborn lung and thereby facilitate edema formation (Table 3) and result in death (Figure 5). Bland teaches that in cases of left ventricular outflow obstruction, hence left ventricular dysfunction, the heart fails and left atrial pressure increases causing elevated pressure in the microcirculature of the lungs often resulting in pulmonary edema (page 93, Pulmonary microvascular hypertension). Increased pulmonary blood flow may lead to edema (page 93, right column).

Jaypee teaches pediatric and neonatal mechanical ventilation and that iNO can be used in hypoxic conditions of the newborn/neonate such as pulmonary hypertenstion (page 156, summary). Jaypee teaches that the adverse effects of iNO in patients with elevated pulmonary capillary wedge pressure with left ventricular dysfunction can lead to **pulmonary edema** (pages 155-156).

Wyka et al. teach uses of iNO for the newborn, including pulmonary hypertension and hypoxemic respiratory distress of the newborn (Table 16-12). In Table 16-13, **Wyka et al. teach that pulmonary edema is an adverse effect of nitric oxide therapy**. Wyka et al. teach that doses less than 20 ppm show minimum adverse effects (page 503, right column). Wyka et al. describe the practitioner of iNO therapy in the summary as being well versed in all aspects of therapy and has critical thinking skills which are vital:

> Medical gas therapy is an integral part of respiratory care practice. The competent, skilled practitioner is well versed in all aspects of therapy. Patient assessment and critical thinking skills are vital, as are skills in equipment selection and troubleshooting. The goals, indications, physiological effects, hazards, and side effects of therapy must always be considered and recognized. These factors, along with documented outcomes assessment, will reflect not only a competent practitioner but also a professional one—one able to interact successfully with other members of the health care team and to actively contribute to the diagnosis, treatment, and recovery of the patient.

Greenough is generally directed to neonatal respiratory disorders and discuss nitric oxide and inhaled nitric oxide therapy with 20 ppm NO producing improvement in oxygenation in term infants with PPHN as well as preterm infants for whom the treatment is an indication if they have hypoxic respiratory failure usually with an OI greater than 25 (pages 183-184 and page 187). Discontinuing a trial of iNO is taught (page 184) as well as weaning infants from iNO (page 184). With respect to contraindications, Greenhough clearly set forth that severe left ventricular dysfunction is

absolutely contraindicated (page 187) as highlighted by the Examiner below for Applicant's benefit:

CONTRAINDICATIONS

Absolute contraindications are hypoxemia secondary to congenital heart disease, right ventricle-dependent circulation, severe left ventricle dysfunction, duct-dependent circulation and methemoglobinemia.

Thus, the art makes it clear that if a neonatal patient has severe left ventricle dysfunction, then iNO is contraindicated.

Greenough also teaches that **pulmonary edema** can occur in the infant due to all forms of left ventricular dysfunction leading to left atrial hypertension (page 392, left column) and the plasma oncotic pressure is normally around 25 mmHg, higher than the pulmonary capillary pressure of about 7-12 mmHg (page 392, left column). Greenough teach that causes of pulmonary edema can be diagnosed from an echocardiogram or electrocardiogram (page 392, right column).

Marter discusses persistent pulmonary hypertension of the newborn (page 377, lower right) which is epidemiologically associated with left ventricular dysfunction (pages 378-379). Marter discusses diagnosis (bottom page 379) with ECG, echocardiogram or other procedures (page 380, D-G) and expressly states that left ventricular dysfunction needs to be ruled out as a competing condition (page 380, G). Marter discusses management with supplemental oxygen (page 380, V.A-page 381), intubation and

mechanical ventilation, ECMO, sedation, metabolic alkalosis, hemodynamic support and inhaled NO (page 381-382, B-G). Marter teaches administration of 20 ppm NO to improve oxygenation or decrease a lability (page 381-382, C) which can occur over 3-4 days (top of page 382). Marter teaches that not all infants respond to iNO and therefore treatment should be at centers with ECMO (page 382). Thus it is implicit that one should discontinue iNO therapy in certain conditions. Marter also teach that iNO can cause other adverse conditions such as methemoglobinemia which should be monitored (page 382).

Summary:

- It is well known in the art to administer 20 ppm iNO to term/near-term neonates to treat hypoxic respiratory failure.
- It is well known in the art that if the neonate has severe left ventricular dysfunction, then iNO is contraindicated.
- It is well known in the art to use diagnostic processes such as echocardiography to determine left ventricular dysfunction in neonates with hypoxic respiratory failure.
- It is well known in the art that iNO can cause pulmonary edema.
- It is well known in the art that left ventricular dysfunction can cause pulmonary edema.
- It is well known in the art to treat neonates with hypoxic respiratory failure with other therapies than iNO.

Ascertainment of the difference between the prior art and the claims

(MPEP 2141.02)

1. The difference between the instant application and Zapol is that Zapol do not expressly teach determining if the first patient does not have pre-existing left ventricular dysfunction and administering 20 ppm iNO for 14 days or until the first patient's hypoxia is resolved and determining a second patient has pre-existing left ventricular dysfunction so as at particular risk of pulmonary edema upon treatment with iNO and administering a second treatment regimen that does not comprise iNO for 14 days or iNO until the hypoxia has resolved but does comprise one or more therapies selected from vasodilators, iv fluids, bicarbonate therapy and mechanical ventilation. This deficiency in Zapol is cured by the teachings of Marter, Bland, Wyka, Jaypee and Greenough.

2. The difference between the instant application and Zapol is that Zapol do not expressly teach determining the patient's PCWP increased during the treatment. This deficiency in Zapol is cured by the teachings of Bland, Wyka, Marter, Jaypee and Greenough.

Level of Ordinary Skill in the Art

(MPEP 2141.03)

The "hypothetical 'person having ordinary skill in the art' to which the claimed subject matter pertains would, of necessity have the capability of understanding the scientific and engineering principles applicable to the pertinent art." *Ex parte Hiyamizu*, 10 USPQ2d 1393, 1394 (Bd. Pat. App. & Inter. 1988). The examiner must ascertain what would have been obvious to one of ordinary skill in the art at the time the invention

was made, and not to the inventor, a judge, a layman, those skilled in remote arts, or to geniuses in the art at hand. *Environmental Designs, Ltd. v. Union Oil Co.*, 713 F.2d 693, 218 USPQ 865 (Fed. Cir. 1983), cert. denied, 464 U.S. 1043 (1984).

The level of ordinary skill will often predetermine whether an implicit suggestion exists to modify the prior art. Persons of varying degrees of skill not only possess varying bases of knowledge, they also possess varying levels of imagination and ingenuity in the relevant field, particularly with respect to problem-solving abilities. If the level of skill is low, for example that of a mere technician, then it may be rational to assume that such an artisan would not think to combine references absent explicit direction in a prior art reference. If, however, the level of skill is that of a medical research scientist, as is the case here, then one can assume comfortably that such an educated artisan will draw conventional ideas from medicine, pharmacy, physiology and chemistry— without being told to do so.

Finding of prima facie obviousness

Rational and Motivation (MPEP 2142-2143)

1. It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to perform the method of Zappol by determining if the first patient does not have pre-existing left ventricular dysfunction and administering 20 ppm iNO for 14 days or until the first patient's hypoxia is resolved and discontinuing iNO therapy to a second patient whose PCWP has increased**,** as suggested by Marter, Bland, Wyka, Jaypee and Greenough, and produce the instant invention.

One of ordinary skill in the art would have been motivated to do this because iNO is contraindicated for infants with severe left ventricular dysfunction (LVD) as taught by Greenough and the artisan would diagnose for LVD to screen for patients with LVD and exclude them from iNO therapy because of the possible risk of pulmonary edema as taught by Jaypee or other risks of serious adverse events of iNO therapy such as methemoglobinemia and consequently apply another known therapy that does not include iNO such as those suggested by Marter including sodium bicarbonate, ECMO and mechanical ventilation (page 382). The artisan understands that by increasing the blood flow by performing the method of Zapol, there is an increased risk of pulmonary edema as suggested by Bland, Wyka and Jaypee. The duration of treatment for 14 days or until the first patient's hypoxia is resolved is a normal endpoint of treatment determined by the physician. Discontinuing treatment of iNO is a decision of the physicians based upon the patient's lack of response to iNO, which would be known immediately by monitoring oxygenation in the patient; hence the hypoxia is not resolved, as taught by Greenough (page 184) or increase in PCWP which will lead to pulmonary edema as taught by Greenough and Jaypee. Thus, increase in PCWP or pulmonary edema itself are indications to discontinue iNO therapy before 14 days or the hypoxia has been resolved for the patient's benefit. The Examiner notes that the ordinary artisan in the iNO art is skilled and has critical thinking skills as taught by Wyka: Wyka et al. describe the practitioner of iNO therapy in the summary as being well versed in all aspects of therapy and has critical thinking skills which are vital:

> Medical gas therapy is an integral part of respiratory care practice. The competent, skilled practitioner is well versed in all aspects of therapy. Patient assessment and critical thinking skills are vital, as are skills in equipment selection and troubleshooting. The goals, indications, physiological effects, hazards, and side effects of therapy must always be considered and recognized. These factors, along with documented outcomes assessment, will reflect not only a competent practitioner but also a professional one—one able to interact successfully with other members of the health care team and to actively contribute to the diagnosis, treatment, and recovery of the patient.

Thus, the ordinary artisan can make the instantly claimed determinations based on the facts at hand and discontinue iNO treatment at any time period including before 14 days or before the hypoxia has resolved for the patients benefit and reduce the risk of pulmonary edema, if it has not already produced pulmonary edema, which is a known outcome of increased PCWP.

Consequently, it is obvious for the ordinary artisan to screen term or near-term neonates who have hypoxic respiratory failure for pre-existing LVD with an echocardiogram to reduce the risk of inducing pulmonary edema or other serious adverse events from iNO and those patients who have pre-existing LVD perform some other known treatment regimen such as mechanical ventilation and for those patients without pre-existing LVD administer 20 ppm NO until the hypoxia is treated or 14 days.

2. It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to perform the method of Zappol by determining the patient's PCWP

increased during the treatment**,** as suggested by Bland, Wyka, Marter, Jaypee and Greenough, and produce the instant invention.

One of ordinary skill in the art would have been motivated to do this because Zapol warns that when the capillary wedge pressure increases pulmonary edema can result that can be fatal (column 2, lines 7-30). Indeed, Zapol suggests various direct and indirect monitoring methods such as ultrasound and Doppler techniques (echocardiography) to measure the pulmonary artery pressure (column 12, lines 56-67). An increase in PCWP will lead to pulmonary edema as taught by Greenough and Jaypee. Thus PCWP is an obvious metric to measure during treatment to avoid the risk of pulmonary edema. As noted above, the ordinary artisan in this art has critical thinking skills and can make decisions based upon the facts at hand. Therefore, it is conventional practice to monitor PWCP as a means to avoid pulmonary edema by the ordinary artisan.

In light of the forgoing discussion, the Examiner concludes that the subject matter defined by the instant claims would have been obvious within the meaning of 35 USC 103(a).

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ernst V. Arnold whose telephone number is 571-272-8509. The examiner can normally be reached on M-F (7:15 am-4:45 pm).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brian Kwon can be reached on 571-272-0581. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Ernst V Arnold/
Primary Examiner, Art Unit 1613

Notice of References Cited	Application/Control No. 14/454,373	Applicant(s)/Patent Under Reexamination BALDASSARRE, JAMES S.	
	Examiner ERNST V. ARNOLD	Art Unit 1613	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
*	A	US-5,570,683	11-1996	Zapol, Warren M.	128/200.14
	B	US-			
	C	US-			
	D	US-			
	E	US-			
	F	US-			
	G	US-			
	H	US-			
	I	US-			
	J	US-			
	K	US-			
	L	US-			
	M	US-			

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	Bland (Acta Paediatr Scand. 1983, Suppl 305:92-99)
	V	Jaypee (Pediatric and Neonatal Mechanical Ventilation 2006, Jaypee Brothers Publishers, Khilnani pages 155-156)
	W	Greenough (Neonatal Respiratory Disorders 2003, 2ed; CRC Press: pages 183-187 and 392)
	X	Wyka et al. (Foundations of Respiratory Care, Cengage Learning, 2002:pages 503-504)

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
S1	5176	((inhalation or inhaled) and ((nitric adj oxide) or (nitrogen adj monoxide)) and (hypoxia or hypoxemic or hypertension or pulmonary) and (baby or newborn or neonate or neonatal or infant))	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2015/04/27 15:11
S2	3299	S1 and @ad<"20090630"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2015/04/27 15:12
S3	85	S2 and (((nitric adj oxide) or (nitrogen adj monoxide)) and (baby or newborn or neonate or neonatal or infant)).clm.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2015/04/27 15:12
S4	42	S3 and (inhale or inhalation or breathe).clm.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2015/04/27 15:13
S5	6	S4 and (("10" or "20" or "30" or "40" or "80") with ppm)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2015/04/27 15:15
S6	1	"5570683".pn. and (baby or neonatal or neonate or newborn or infant)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2015/04/27 15:16
S7	1	"5570683".pn. and (baby or neonatal or neonate or newborn or infant) and (hypoxic or hypoxia or hypoxemic)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2015/04/27 15:17
S8	1	S7 and (("10" or "20" or "30" or "40" or "80") with ppm)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2015/04/27 15:18
S9	1	"14454373" and (hypoxic with pulmonary)	US-PGPUB; USPAT;	OR	ON	2015/04/27 15:23

			USOCR; FPRS; EPO; JPO; DERWENT			

EAST Search History (Interference)

< This search history is empty>

4/ 28/ 2015 5:21:04 PM
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99)**		
	Application Number	14454373
	Filing Date	2014-08-07
	First Named Inventor	Baldassarre
	Art Unit	1613
	Examiner Name	Ernst V. Arnold
	Attorney Docket Number	26047-0003011

U.S.PATENTS						Remove
Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	8282966		2012-10-09	Baldassarre et al.	
	2	8846112		2014-09-30	Baldassarre	
	3	8293284		2012-10-23	Baldassare	
	4	8431163		2013-04-30	Baldassarre	
	5	8795741		2014-08-05	Baldassarre	
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Receipt date: 02/06/2015	Application Number	14454373 14454373 - GAU: 1613
INFORMATION DISCLOSURE STATEMENT BY APPLICANT	Filing Date	2014-08-07
	First Named Inventor	Baldassarre
(Not for submission under 37 CFR 1.99)	Art Unit	1613
	Examiner Name	Ernst V. Arnold
	Attorney Docket Number	26047-0003011

Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2] i	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]
	1							☐

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NON-PATENT LITERATURE DOCUMENTS Remove

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]
	1	Goyal et al., "Efficacy of nitroglycerin inhalation in reducing pulmonary arterial hypertension in children with congenital heart disease," British Journal of Anaesthesia, 97(2):208-214 (May 2006)	☐
	2	Pozzoli et al., "Non-invasive Estimation of Left Ventricular Filling Pressures by Doppler Echocardiography," Eur J Echocardiography, 3:75-79 (March 2002)	☐
	3	"Safety: What is a Serious Adverse Event?" Retrieved from the Internet:<URL:http://www.fda.gov/Safety/MedWatch/HowToReport/ucm053087.htm> (June 11, 2009)	☐
	4	Center for Drug Evaluation and Research, "NO Labeling," Application Number NDA 20845, [retrieved on August 8, 2000], Retrieved from the Internet:<URL:http://www.fda.gov/cder/foi/label/1999/208451bl.htm> (1999)	☐
	5	Klabunde, "Cardiovascular Physiology Concepts: Pulmonary Capillary Wedge Pressure," [retrieved on May 8, 2014] Retrieved from the Internet:<URL:http://www.cvphysiology.com/Heart%20Failure/HF008.htm> (June 2, 2009)	☐
	6	Hoehn, "Therapy of pulmonary hypertension in neonates and infants," Pharmacology & Therapeutics, 114:318-326 (June 2007)	☐
	7	Ivy et al., "Pediatric Pulmonary Hypertension," J Am Coll Cardiol, 62:D117-126 (October 2013)	☐

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /E.A./

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	Attorney Docket Number	26047-0003011

	8	Simonneau et al., "Clinical Classification of Pulmonary Hypertension," J Am Coll Cardiol, 43:5S-12S (February 2004)	☐
	9	Simonneau et al., "Updated Clinical Classification of Pulmonary Hypertension," J Am Coll Cardiol, 54(1):S43-54 (April 2009)	☐
	10	Webster's Third New International Dictionary of the English Language Unabridged, Philip Babcok Gove Editor in Chief, Merriam-Webster Inc.: Springfield, Massachusetts, page 388 (2002)	☐
	11	Waldmann et al., "Oxygen Therapy," Oxford Desk Reference Critical Care, Oxford University Press: Oxford, New York, pp. 2-4 (2008)	☐
	12	Wessel, David L., "Commentary: Simple Gases and Complex Single Ventricles," J Thorac Cardiovasc Surg, 112:655-657 (June 1996)	☐
	13	Ware, Linda E., "Inhaled Nitric Oxide in Infants and Children," Critical Care Nursing Clinics of North America, 14(1):1-6 (March 2002)	☐
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ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /E.A./

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	20	Chemla et al., "Series 'Advances in Pathobiology, Diagnosis, and Treatment of Pulmonary Hypertension'; Hemodynamic evaluation of Pulmonary Hypertension", Eur Respir J 20:1314-1331 (August 2002)	☐
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	22	Cloherty et al., editors, Manual of Neonatal Care, 5th edition, pages 377-383 (2004)	☐
	23	PRAXAIR DISTRIBUTION V. INO THERAPEUTICS, INC. d/b/a IKARIA, INC., Petition for InterPartes Review of U.S. Patent No. 8,282,966 dated January 5, 2015 (255 pages)	☐
	24	PRAXAIR DISTRIBUTION V. INO THERAPEUTICS, INC. d/b/a IKARIA, INC., Petition for InterPartes Review of U.S. Patent No. 8,293,284 dated January 5, 2015 (251 pages)	☐
	25	Simonneau et al., "Updated Clinical Classification of Pulmonary Hypertension," J Am Coll Cardiol, 62(25):D34-41 (October 2013)	☐
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	27	PRAXAIR DISTRIBUTION V. INO THERAPEUTICS, INC. d/b/a IKARIA, INC., Petition for InterPartes Review of U.S. Patent No. 8,846,112 dated January 5, 2015 (280 pages)	☐
	28	PRAXAIR DISTRIBUTION V. INO THERAPEUTICS, INC. d/b/a IKARIA, INC., Petition for InterPartes Review of U.S. Patent No. 8,431,163 dated January 5, 2015 (223 pages)	☐
	29	PRAXAIR DISTRIBUTION V. INO THERAPEUTICS, INC. d/b/a IKARIA, INC., Petition for InterPartes Review of U.S. Patent No. 8,795,741 dated January 5, 2015 (382 pages)	☐

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	Examiner Name	Ernst V. Arnold
	Attorney Docket Number	26047-0003011

	30	Juliana et al., "Severe persistent pulmonary hypertension of the newborn in a setting where limited resources exclude the use of inhaled nitric oxide: successful treatment with sildenafil," Eur J Pediatr, 164:626-629 (July 2005)	☐

If you wish to add additional non-patent literature document citation information please click the Add button **Add**

EXAMINER SIGNATURE

Examiner Signature	/Ernst Arnold/	Date Considered	04/20/2015

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /E.A./

Receipt date: 02/06/2015	Application Number	14454373	14454373 - GAU: 1613
INFORMATION DISCLOSURE STATEMENT BY APPLICANT	Filing Date	2014-08-07	
(Not for submission under 37 CFR 1.99)	First Named Inventor	Baldassarre	
	Art Unit	1613	
	Examiner Name	Ernst V. Arnold	
	Attorney Docket Number	26047-0003011	

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☐ See attached certification statement.

☐ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Janis K. Fraser/	Date (YYYY-MM-DD)	2015-02-06
Name/Print	Janis K. Fraser	Registration Number	34819

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these record s.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /E.A./

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14454373	BALDASSARRE, JAMES S.
	Examiner	Art Unit
	ERNST V ARNOLD	1613

CPC- SEARCHED		
Symbol	Date	Examiner

CPC COMBINATION SETS - SEARCHED		
Symbol	Date	Examiner

US CLASSIFICATION SEARCHED			
Class	Subclass	Date	Examiner
424	718 text limited	11/5/14	eva

SEARCH NOTES		
Search Notes	Date	Examiner
inventor/assignee name EAST/PALM	9/8/14	eva
EAST	9/8/14	eva
updated IDS	10/14/14	eva
search update EAST	11/5/14	eva
search update EAST	4/28/15	eva

INTERFERENCE SEARCH			
US Class/ CPC Symbol	US Subclass / CPC Group	Date	Examiner
424	718 text limited	11/5/14	eva

U.S. DEPARTMENT OF COMMERCE
PATENT AND TRADEMARK OFFICE

PATENT WITHDRAWAL NOTICE

DATE WITHDRAWN	WITHDRAWAL NUMBER
2/10/2015	28084

The following application has been **WITHDRAWN** from the

2/10/2015 issue.

SERIAL NO.	PATENT NUMBER
14454373	8951580

TITLE

METHODS FOR IMPROVING THE SAFETY OF TREATING PEDIATRIC PATIENTS WHO ARE CANDIDATES FOR INHALED NITRIC OXIDE TREATMENT

NAME AND ADDRESS

JAMES BALDASSARRE
Doylestown, PA

REASON FOR WITHDRAWAL

Auto-petition to withdraw - Granted

-

APPROVED

/Kimberly Terrell/, Manager

Patent Publication Branch
Office of Data Management

FORM PTO-302 -- (REV. 05-2009)

PTO/SB/30 (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Request for Continued Examination (RCE) Transmittal

Address to:
Mail Stop RCE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Application Number	14/454,373
Filing Date	August 7, 2014
First Named Inventor	James S. Baldassarre
Art Unit	1613
Examiner Name	Ernst V. Arnold
Attorney Docket Number	26047-0003011

This is a Request for Continued Examination (RCE) under 37 CFR 1 .114 of the above-identified application.
Request for Continued Examination (RCE) practice under 37 CFR 1.114 does not apply to any utility or plant application filed prior to June 8, 1995, or to any design application. See Instruction Sheet for RCEs (not to be submitted to the USPTO) on page 2.

1. Submission required under 37 CFR 1.114 Note: If the RCE is proper, any previously filed unentered amendments and amendments enclosed with the RCE will be entered in the order in which they were filed unless applicant instructs otherwise. If applicant does not wish to have any previously filed unentered amendment(s) entered, applicant must request non-entry of such amendment(s).

   a. ☐ Previously submitted. If a final Office action is outstanding, any amendments filed after the final Office action may be considered as a submission even if this box is not checked.

      i. ☐ Consider the arguments in the Appeal Brief or Reply Brief previously filed on _____

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   b. ☒ Enclosed

      i. ☐ Amendment/Reply

      ii. ☐ Affidavit(s)/ Declaration(s)

      iii. ☒ Information Disclosure Statement (IDS)

      iv. ☐ Other _____

2. Miscellaneous

   Suspension of action on the above-identified application is requested under 37 CFR 1.103(c) for a

   a. ☐ period of _____ months. (Period of suspension shall not exceed 3 months; Fee under 37 CFR 1.17(i) required)

   b. ☐ Other _____

3. Fees The RCE fee under 37 CFR 1.17(e) is required by 37 CFR 1.114 when the RCE is filed.
   The Director is hereby authorized to charge the following fees any underpayment of fees or credit any overpayments to

   a. ☒ Deposit Account No. 06-1050 .

      i. ☒ RCE fee required under 37 CFR 1.17(e)

      ii ☐ Extension of time fee (37 CFR 1.136 and 1.17)

      iii ☒ Other any deficiencies

   b. ☐ Check in the amount of $ _____ enclosed

   c. ☐ Payment by credit card (Form PTO-2038 enclosed)

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT REQUIRED

Signature	/Janis K. Fraser/	Date	February 6, 2015
Name (Print/Type)	Janis K. Fraser, Ph.D., J.D.	Registration No.	34,819

CERTIFICATE OF MAILING OR TRANSMISSION

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Signature			
Name (Print/Type)		Date	

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Named Inventor	:	James S. Baldassarre	Art Unit	:	1613
Serial No.	:	14/454,373	Examiner	:	Ernst V. Arnold
Filed	:	August 7, 2014	Conf. No.	:	3860
Title	:	METHODS FOR IMPROVING THE SAFETY OF TREATING PATIENTS WHO ARE CANDIDATES FOR INHALED NITRIC OXIDE TREATMENT			

MAIL STOP RCE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

EIGHTH INFORMATION DISCLOSURE STATEMENT

Please consider the references listed on the enclosed PTO-SB-08 Form. The non-patent literature is enclosed; the cited U.S. patents will be provided on request.

The enclosed PTO-SB-08 Form lists five Petitions for *Inter Partes* Review filed in five patents related to the present application: US Patent Nos. 8,282,966; 8,293,284; 8,431,163; 8,795,741; and 8,846,112. The Form also lists documents submitted as Exhibits in the various Petitions. Certain of the documents submitted as Exhibits in the Petitions have been previously made of record in this application, so are not listed on the present PTO-SB-08 Form nor re-submitted with this filing. For the Examiner's convenience, the Exhibit documents previously made of record are listed below, with an indication of the previous Information Disclosure Statement where each such document was cited. Additional copies of the below documents will be provided on request.

Bernasconi et al.; Inhaled Nitric Oxide Applications in Pediatric Practice, Images in Pediatric Cardiology, Vol. 4(1), Jan-Mar 2002; pages 4-29. – ***cited in Sixth IDS (filed 8/25/2014)***

Davidson et al., "Inhaled nitric oxide for the early treatment of persistent pulmonary hypertension of the term newborn: a randomized, double-masked, placebo-controlled, dose-response, multicenter study," Pediatrics, Vol. 101 (3 Pt 1), pages 325-34 (1998) – ***cited in First IDS (filed 8/7/2014)***

Loh et al., "Cardiovascular Effects of Inhaled Nitric Oxide in Patients with Left Ventricular Dysfunction," Circulation, Vol. 90, pages 2780-2785 (1994) – ***cited in Third IDS (filed 8/13/2014)***

Macrae et al., "Inhaled nitric oxide therapy in neonates and children: reaching a European consensus," Intensive Care Med., Vol. 30, pages 372-380 (2004) – ***cited in Third IDS (filed 8/13/2014)***

Ichinose et al., "Inhaled Nitric Oxide - A Selective Pulmonary Vasodilator: Current Uses and Therapeutic Potential," Circulation, Vol. 109, pages 3106-3111 (2004) – ***cited in Second IDS (filed 8/8/2014)***

Ehrenkranz, "Inhaled Nitric Oxide in Full-Term and Nearly Full-Term Infants with Hypoxic Respiratory Failure," The Neonatal Inhaled Nitric Oxide Study Group, N. Engl. J. Med., Vol. 336, No. 9, pages 597-605 (1997) – ***cited in First IDS (filed 8/7/2014)***

Henrichsen et al., "Inhaled Nitric Oxide Can Cause Severe Systemic Hypotension," Journal of Pediatrics, Mosby-Year Book, St. Louis, MO, Vol. 129, No. 1, page 183 (1996) – ***cited in Second IDS (filed 8/8/2014)***

The file histories of the patents that are the subject of the Petitions are among the Exhibits listed in the Petitions; since these file histories are available to the Examiner via PAIR, they are not submitted with this IDS. The Declaration of Dr. Maurice Beghetti, CV of Dr. Beghetti, and claim charts listed as Exhibits in the Petitions are not separately listed on the enclosed PTO-SB-08 Form, but are appended to the Petition documents that are submitted with this IDS so that they are available for the Examiner's review.

This IDS is being filed with a Request for Continued Examination, so no IDS fee is required. Apply any necessary charges or credits to deposit account 06-1050, referencing the above attorney docket number.

Respectfully submitted,

Date: February 6, 2015

/Janis K. Fraser/
Janis K. Fraser, Ph.D., J.D.
Reg. No. 34,819

Customer Number 94169
Fish & Richardson P.C.
Telephone: (617) 542-5070
Facsimile: (877) 769-7945

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Doc code: IDS
Doc description: Information Disclosure Statement (IDS) Filed

PTO/SB/08a (01-10)
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99)**		
	Application Number	14454373
	Filing Date	2014-08-07
	First Named Inventor	Baldassarre
	Art Unit	1613
	Examiner Name	Ernst V. Arnold
	Attorney Docket Number	26047-0003011

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	3	8293284		2012-10-23	Baldassare	
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	14454373
	Filing Date	2014-08-07
	First Named Inventor	Baldassarre
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	Examiner Name	Ernst V. Arnold
	Attorney Docket Number	26047-0003011

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	1	Goyal et al., "Efficacy of nitroglycerin inhalation in reducing pulmonary arterial hypertension in children with congenital heart disease," British Journal of Anaesthesia, 97(2):208-214 (May 2006)	☐
	2	Pozzoli et al., "Non-invasive Estimation of Left Ventricular Filling Pressures by Doppler Echocardiography," Eur J Echocardiography, 3:75-79 (March 2002)	☐
	3	"Safety: What is a Serious Adverse Event?" Retrieved from the Internet:<URL:http://www.fda.gov/Safety/MedWatch/HowToReport/ucm053087.htm> (June 11, 2009)	☐
	4	Center for Drug Evaluation and Research, "NO Labeling," Application Number NDA 20845, [retrieved on August 8, 2000], Retrieved from the Internet:<URL:http://www.fda.gov/cder/foi/label/1999/208451bl.htm> (1999)	☐
	5	Klabunde, "Cardiovascular Physiology Concepts: Pulmonary Capillary Wedge Pressure," [retrieved on May 8, 2014] Retrieved from the Internet:<URL:http://www.cvphysiology.com/Heart%20Failure/HF008.htm> (June 2, 2009)	☐
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	7	Ivy et al., "Pediatric Pulmonary Hypertension," J Am Coll Cardiol, 62:D117-126 (October 2013)	☐

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	Examiner Name	Ernst V. Arnold
	Attorney Docket Number	26047-0003011

	8	Simonneau et al., "Clinical Classification of Pulmonary Hypertension," J Am Coll Cardiol, 43:5S-12S (February 2004)	☐
	9	Simonneau et al., "Updated Clinical Classification of Pulmonary Hypertension," J Am Coll Cardiol, 54(1):S43-54 (April 2009)	☐
	10	Webster's Third New International Dictionary of the English Language Unabridged, Philip Babcok Gove Editor in Chief, Merriam-Webster Inc.: Springfield, Massachusetts, page 388 (2002)	☐
	11	Waldmann et al., "Oxygen Therapy," Oxford Desk Reference Critical Care, Oxford University Press: Oxford, New York, pp. 2-4 (2008)	☐
	12	Wessel, David L., "Commentary: Simple Gases and Complex Single Ventricles," J Thorac Cardiovasc Surg, 112:655-657 (June 1996)	☐
	13	Ware, Linda E., "Inhaled Nitric Oxide in Infants and Children," Critical Care Nursing Clinics of North America, 14(1):1-6 (March 2002)	☐
	14	Jonsen et al., Clinical Ethics: A Practical Approach to Ethical Decisions in Clinical Medicine, "The Goals and Benefits of Medicine," McGraw-Hill, pages 15-32 (1998)	☐
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	16	Hoeper et al., " Definitions and Diagnosis of Pulmonary Hypertension," Journal of the American College of Cardiology, 62(25):D42-50 (October 2013)	☐
	17	Ignarro et al., Nitric Oxide Biology and Pathobiology, Academic Press, Chapter 56 ("Clinical Therapy with Inhaled Nitric Oxide in Respiratory Diseases"), pages 931-933, 940-941; Chapter 58 ("Nitric Oxide and Persistent Pulmonary Hypertension in the Newborn"), pages 963, 970-978 (2000)	☐
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	Attorney Docket Number	26047-0003011

	19	Griffiths and Evans, "Inhaled Nitric Oxide Therapy in Adults," N Engl J Med, 353:2683-2695 (December 2005)	☐
	20	Chemla et al., "Series 'Advances in Pathobiology, Diagnosis, and Treatment of Pulmonary Hypertension'; Hemodynamic evaluation of Pulmonary Hypertension", Eur Respir J 20:1314-1331 (August 2002)	☐
	21	Gittler and Goldstein, "The Elements of Medical Malpractice: An Overview," Clinical Infectious Diseases, 23:1152-1155 (June 1996)	☐
	22	Cloherty et al., editors, Manual of Neonatal Care, 5th edition, pages 377-383 (2004)	☐
	23	PRAXAIR DISTRIBUTION V. INO THERAPEUTICS, INC. d/b/a IKARIA, INC., Petition for InterPartes Review of U.S. Patent No. 8,282,966 dated January 5, 2015 (255 pages)	☐
	24	PRAXAIR DISTRIBUTION V. INO THERAPEUTICS, INC. d/b/a IKARIA, INC., Petition for InterPartes Review of U.S. Patent No. 8,293,284 dated January 5, 2015 (251 pages)	☐
	25	Simonneau et al., "Updated Clinical Classification of Pulmonary Hypertension," J Am Coll Cardiol, 62(25):D34-41 (October 2013)	☐
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	27	PRAXAIR DISTRIBUTION V. INO THERAPEUTICS, INC. d/b/a IKARIA, INC., Petition for InterPartes Review of U.S. Patent No. 8,846,112 dated January 5, 2015 (280 pages)	☐
	28	PRAXAIR DISTRIBUTION V. INO THERAPEUTICS, INC. d/b/a IKARIA, INC., Petition for InterPartes Review of U.S. Patent No. 8,431,163 dated January 5, 2015 (223 pages)	☐
	29	PRAXAIR DISTRIBUTION V. INO THERAPEUTICS, INC. d/b/a IKARIA, INC., Petition for InterPartes Review of U.S. Patent No. 8,795,741 dated January 5, 2015 (382 pages)	☐

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	14454373
	Filing Date	2014-08-07
	First Named Inventor	Baldassarre
	Art Unit	1613
	Examiner Name	Ernst V. Arnold
	Attorney Docket Number	26047-0003011

	30	Juliana et al., "Severe persistent pulmonary hypertension of the newborn in a setting where limited resources exclude the use of inhaled nitric oxide: successful treatment with sildenafil," Eur J Pediatr, 164:626-629 (July 2005)	☐

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Examiner Signature		Date Considered	

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[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	14454373
	Filing Date	2014-08-07
	First Named Inventor	Baldassarre
	Art Unit	1613
	Examiner Name	Ernst V. Arnold
	Attorney Docket Number	26047-0003011

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☐ See attached certification statement.

☐ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Janis K. Fraser/	Date (YYYY-MM-DD)	2015-02-06
Name/Print	Janis K. Fraser	Registration Number	34819

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

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7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Doc Code: PET.AUTO Document Description: Petition automatically granted by EFS-Web	PTO/SB/140 U.S. Patent and Trademark Office Department of Commerce

Electronic Petition Request	**PETITION TO WITHDRAW AN APPLICATION FROM ISSUE AFTER PAYMENT OF THE ISSUE FEE UNDER 37 CFR 1.313(c)**
Application Number	14454373
Filing Date	07-Aug-2014
First Named Inventor	James Baldassarre
Art Unit	1613
Examiner Name	ERNST ARNOLD
Attorney Docket Number	26047-0003011
Title	METHODS FOR IMPROVING THE SAFETY OF TREATING PEDIATRIC PATIENTS WHO ARE CANDIDATES FOR INHALED NITRIC OXIDE TREATMENT

An application may be withdrawn from issue for further action upon petition by the applicant. To request that the Office withdraw an application from issue, applicant must file a petition under this section including the fee set forth in § 1.17(h) and a showing of good and sufficient reasons why withdrawal of the application from issue is necessary.

APPLICANT HEREBY PETITIONS TO WITHDRAW THIS APPLICATION FROM ISSUE UNDER 37 CFR 1.313(c).

A grantable petition requires the following items:
(1) Petition fee; and
(2) One of the following reasons:
(a) Unpatentability of one or more claims, which must be accompanied by an unequivocal statement that one or more claims are unpatentable, an amendment to such claim or claims, and an explanation as to how the amendment causes such claim or claims to be patentable;
(b) Consideration of a request for continued examination in compliance with § 1.114 (for a utility or plant application only); or
(c) Express abandonment of the application. Such express abandonment may be in favor of a continuing application, but not a CPA under 37 CFR 1.53(d).

Petition Fee

- (◉) Small Entity
- ( ) Micro Entity
- ( ) Regular Undiscounted

Reason for withdrawal from issue

○ One or more claims are unpatentable ◉ Consideration of a request for continued examination (RCE) (List of Required Documents and Fees) ○ Applicant hereby expressly abandons the instant application (any attorney/agent signing for this reason must have power of attorney pursuant to 37 CFR 1.32(b)).	
RCE request,submission, and fee. ☐ I certify, in accordance with 37 CFR 1.4(d)(4) that : The RCE request ,submission, and fee have already been filed in the above-identified application on ☒ Are attached.	
THIS PORTION MUST BE COMPLETED BY THE SIGNATORY OR SIGNATORIES I certify, in accordance with 37 CFR 1.4(d)(4) that I am: ◉ An attorney or agent registered to practice before the Patent and Trademark Office who has been given power of attorney in this application. ○ An attorney or agent registered to practice before the Patent and Trademark Office, acting in a representative capacity. ○ A sole inventor ○ A joint inventor; I certify that I am authorized to sign this submission on behalf of all of the inventors as evidenced by the power of attorney in the application ○ A joint inventor; all of whom are signing this e-petition	
Signature	/Tiffany Reiter/
Name	Tiffany Reiter
Registration Number	61359

Electronic Patent Application Fee Transmittal

Application Number:	14454373
Filing Date:	07-Aug-2014
Title of Invention:	METHODS FOR IMPROVING THE SAFETY OF TREATING PEDIATRIC PATIENTS WHO ARE CANDIDATES FOR INHALED NITRIC OXIDE TREATMENT
First Named Inventor/Applicant Name:	James S. Baldassarre
Filer:	Janis K. Fraser/Tiffany Reiter
Attorney Docket Number:	26047-0003011

Filed as Small Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Petition Fee-37CFR 1.17(h) (Group II)	2464	1	70	70
Request for Continued Examination	2801	1	600	600
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Miscellaneous:				
		Total in USD ($)		**670**

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Decision Date : February 6, 2015

In re Application of :

James Baldassarre

DECISION ON PETITION

UNDER CFR 1.313(c)(2)

Application No : 14454373

Filed : 07-Aug-2014

Attorney Docket No : 26047-0003011

This is an electronic decision on the petition under 37 CFR 1.313(c)(2), filed February 6, 2015 , to withdraw the above-identified application from issue after payment of the issue fee.

The petition is **GRANTED.**

The above-identified application is withdrawn from issue for consideration of a submission under 37 CFR 1.114 (request for continued examination). See 37 CFR 1.313(c)(2).

Petitioner is advised that the issue fee paid in this application cannot be refunded. If, however, this application is again allowed, petitioner may request that it be applied towards the issue fee required by the new Notice of Allowance.

Telephone inquiries concerning this decision should be directed to the Patent Electronic Business Center (EBC) at 866-217-9197.

This application file is being referred to Technology Center AU 1613 for processing of the request for continuing examination under 37 CFR 1.114 .

Office of Petitions

Electronic Acknowledgement Receipt	
EFS ID:	21428399
Application Number:	14454373
International Application Number:	
Confirmation Number:	3860
Title of Invention:	METHODS FOR IMPROVING THE SAFETY OF TREATING PEDIATRIC PATIENTS WHO ARE CANDIDATES FOR INHALED NITRIC OXIDE TREATMENT
First Named Inventor/Applicant Name:	James S. Baldassarre
Customer Number:	94169
Filer:	Janis K. Fraser/Tiffany Reiter
Filer Authorized By:	Janis K. Fraser
Attorney Docket Number:	26047-0003011
Receipt Date:	06-FEB-2015
Filing Date:	07-AUG-2014
Time Stamp:	18:58:51
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$670
RAM confirmation Number	5902
Deposit Account	061050
Authorized User	
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2	Transmittal Letter	IDS.pdf	100982 32aac1e507e0775251aa2b9f52939a22f3bc080b	no	3
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3	Information Disclosure Statement (IDS) Form (SB08)	SB08.pdf	614357 9359fc8149119c2e744a5dc0e71323f1342c01b2	no	7
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Warnings:					
Information:					
24	Non Patent Literature	Gittler.pdf	359466 cfdc08aede21d46ce8822fe427dc6e8d9dd1c5f9	no	4
Warnings:					
Information:					
25	Non Patent Literature	Cloherty.pdf	1658779 6cd10891293993e4580a024b48a484b977744cd6	no	12
Warnings:					
Information:					

26	Non Patent Literature	Petition966.pdf	3342639 65431c3b9bf59c90096edf7977ea9b2234552073	no	255
Warnings:					
Information:					
27	Non Patent Literature	Petition284.pdf	2467232 fc63121e4bb16607b68a81603f9e24abb10d97b9	no	251
Warnings:					
Information:					
28	Non Patent Literature	Simonneau_Updated2013.pdf	1625366 c98ecba37a8093829ece4b82d1fc13e67084ccc2	no	8
Warnings:					
Information:					
29	Non Patent Literature	Germann.pdf	1578018 947fe15950c07ebc53456e5a850775a936c524ba	no	13
Warnings:					
Information:					
30	Non Patent Literature	Petition112.pdf	14599522 8538ec080ecd1daff47753c6515ad3a756e7e248	no	280
Warnings:					
Information:					
31	Non Patent Literature	Petition163.pdf	2235229 0ed9d496a372a14c6a98b8596d209b4bc9faf72c	no	223
Warnings:					
Information:					
32	Non Patent Literature	Petition741.pdf	3607291 e0c6370dd8c4387fcb97af1cc005db480faafbcf	no	382
Warnings:					
Information:					
33	Non Patent Literature	Juliana.pdf	1541163 76b43e659117c10b36427e0d123db1a48c789a3b	no	4
Warnings:					
Information:					
34	Petition automatically granted by EFS	petition-request.pdf	31562 a85f4a20d0c3f941d7b3746b4b88b7fa1006f1dd	no	2
Warnings:					
Information:					

35	Fee Worksheet (SB06)	fee-info.pdf	32634 241042eed2225a95fd10950b050792080d2abb40	no	2

Warnings:	
Information:	
Total Files Size (in bytes):	118468145

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

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United States Patent and Trademark Office
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www.uspto.gov

APPLICATION NO.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/454,373	02/10/2015	8951580	26047-0003011	3860

94169 7590 01/21/2015

Fish & Richardson PC
P.O.Box 1022
minneapolis, MN 55440

ISSUE NOTIFICATION

The projected patent number and issue date are specified above.

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(application filed on or after May 29, 2000)

The Patent Term Adjustment is 0 day(s). Any patent to issue from the above-identified application will include an indication of the adjustment on the front page.

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (http://pair.uspto.gov).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Application Assistance Unit (AAU) of the Office of Data Management (ODM) at (571)-272-4200.

APPLICANT(s) (Please see PAIR WEB site http://pair.uspto.gov for additional applicants):

INO Therapeutics LLC, Hampton, NJ, Assignee (with 37 CFR 1.172 Interest);
James S. Baldassarre, Doylestown, PA;

METHODS FOR IMPROVING THE SAFETY OF TREATING PEDIATRIC PATIENTS WHO ARE CANDIDATES FOR INHALED NITRIC OXIDE TREATMENT

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application is a continuation of U.S. Serial No. 14/451,057, filed August 4, 2014, which is a continuation of U.S. Serial No. 13/683,417 (now U.S. Patent No. 8,795,741), filed November 21, 2012, which is a continuation of U.S. Serial No. 12/820,866, filed June 22, 2010, and now abandoned, which is a continuation of U.S. Serial No. 12/494,598, filed June 30, 2009, and now abandoned. U.S. Serial No. 13/683,417 is also a continuation of U.S. Serial No. 13/651,660 (now U.S. Patent No. 8,431,163), filed October 15, 2012, which is a continuation of U.S. Application Serial No. 12/821,041 (now U.S. Patent No. 8,293,284), filed June 22, 2010, which is a continuation of U.S. Application Serial No. 12/494,598, filed June 30, 2009, and now abandoned. U.S. Serial No. 14/451,057 is also a division of U.S. Application Serial No. 13/683,444, filed November 21, 2012, which is a division of U.S. Application Serial No. 12/820,866, filed June 22, 2010, and now abandoned, which is a continuation of U.S. Application Serial No. 12/494,598, filed June 30, 2009. U.S. Application Serial No. 13/683,444 is also a division of 13/651,660 (now U.S. Patent No. 8,431,163), filed October 15, 2012, which is a continuation of U.S. Application Serial No. 12/821,041 (now U.S. Patent No. 8,293,284), filed June 22, 2010, which is a continuation of U.S. Application Serial No. 12/494,598, filed June 30, 2009, and now abandoned. This application is also a division of 13/683,444, filed November 21, 2012, which is a division of U.S. Application Serial No. 12/820,866, filed June 22, 2010, and now abandoned, which is a continuation of U.S. Application Serial No. 12/494,598, filed June 30, 2009. U.S. Application Serial No. 13/683,444 is also a division of 13/651,660 (now U.S. Patent No. 8,431,163), filed October 15, 2012, which is a continuation of U.S. Application Serial No. 12/821,041 (now U.S. Patent No. 8,293,284), filed June 22, 2010, which is a continuation of U.S. Application Serial No. 12/494,598, filed June 30, 2009, and now abandoned. The contents of the foregoing applications are incorporated by reference in the present application.

STATEMENT CONCERNING GOVERNMENT INTEREST

[0002] Not applicable.

OK to Enter
/EA/
1/5/15

Attorney's Docket No.: 26047-0003011 / 3000-US-0008CON8

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Named Inventor	:	James S. Baldassarre	Conf. No.	: 3860
Serial No.	:	14/454,373		
Filed	:	August 7, 2014		
Title *(as amended)*	:	METHODS FOR IMPROVING THE SAFETY OF TREATING PEDIATRIC PATIENTS WHO ARE CANDIDATES FOR INHALED NITRIC OXIDE TREATMENT		

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

PRELIMINARY AMENDMENT

Track 1 status has been requested for this application. Prior to examination, please amend the application as indicated on the following pages.

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: Mail Mail Stop ISSUE FEE
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
or Fax (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

94169 7590 11/20/2014

FISH & RICHARDSON P.C.
P.O. BOX 1022
MINNEAPOLIS, MN 55440-1022

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO (571) 273-2885, on the date indicated below.

(Depositor's name)

(Signature)

(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/454,373	08/07/2014	James S. Baldassarre	26047-0003011	3860

TITLE OF INVENTION: METHODS FOR IMPROVING THE SAFETY OF TREATING PEDIATRIC PATIENTS WHO ARE CANDIDATES FOR INHALED NITRIC OXIDE TREATMENT

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	SMALL	$480	$0		$480	02/20/2015

EXAMINER	ART UNIT	CLASS-SUBCLASS
ARNOLD, ERNST V.	1613	424-718000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

[ ] Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.

[ ] "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list

(1) the names of up to 3 registered patent attorneys or agents OR, alternatively,

(2) the name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 Fish & Richardson P.C.
2
3

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE: INO Therapeutics LLC

(B) RESIDENCE: (CITY and STATE OR COUNTRY): Hampton, NJ

Please check the appropriate assignee category or categories (will not be printed on the patent): [ ] Individual [X] Corporation or other private group entity [ ] Government

4a. The following fee(s) are submitted:

[X] Issue Fee

[ ] Publication Fee (No small entity discount permitted)

[ ] Advance Order - # of Copies _____

4b. Payment of Fee(s): (**Please first reapply any previously paid issue fee shown above**)

[ ] A check in the amount of the fee(s) is enclosed.

[ ] Payment by credit card. Form PTO-2038 is attached.

[X] The Director is hereby authorized to charge the required fee(s), or credit any overpayment, to Deposit Account Number 06-1050

5. **Change in Entity Status** (from status indicated above)

[ ] Applicant certifying micro entity status. See 37 CFR 1.29 — **NOTE**: Absent a valid certification of Micro Entity Status (see form PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.

[ ] Applicant asserting small entity status. See 37 CFR 1.27. — **NOTE**: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.

[ ] Applicant changing to regular undiscounted fee status. — **NOTE**: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

The Director of the USPTO is requested to apply the Issue Fee and Publication Fee (if any) or to re-apply any previously paid issue fee to the application identified above.
NOTE: The Issue Fee and Publication Fee (if required) will not be accepted from anyone other than the applicant; a registered attorney or agent; or the assignee or other party in interest as shown by the records of the United States Patent and Trademark Office.

Authorized Signature /Janis K. Fraser/ Date December 29, 2014

Typed or printed name Janis K. Fraser, Ph.D., J.D. Registration No. 34,819

23338616.doc

Electronic Patent Application Fee Transmittal

Application Number:	14454373
Filing Date:	07-Aug-2014
Title of Invention:	METHODS FOR IMPROVING THE SAFETY OF TREATING PEDIATRIC PATIENTS WHO ARE CANDIDATES FOR INHALED NITRIC OXIDE TREATMENT
First Named Inventor/Applicant Name:	James S. Baldassarre
Filer:	Janis K. Fraser/Christine Grace
Attorney Docket Number:	26047-0003011

Filed as Small Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Utility Appl Issue Fee	2501	1	480	480

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Miscellaneous:				
		Total in USD ($)		**480**

Electronic Acknowledgement Receipt	
EFS ID:	21076804
Application Number:	14454373
International Application Number:	
Confirmation Number:	3860
Title of Invention:	METHODS FOR IMPROVING THE SAFETY OF TREATING PEDIATRIC PATIENTS WHO ARE CANDIDATES FOR INHALED NITRIC OXIDE TREATMENT
First Named Inventor/Applicant Name:	James S. Baldassarre
Customer Number:	94169
Filer:	Janis K. Fraser/Devon Weide
Filer Authorized By:	Janis K. Fraser
Attorney Docket Number:	26047-0003011
Receipt Date:	29-DEC-2014
Filing Date:	07-AUG-2014
Time Stamp:	15:55:06
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$480
RAM confirmation Number	2247
Deposit Account	061050
Authorized User	
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Post Allowance Communication - Incoming	Response.pdf	62480 108783d5e7fb024e26770175ccb0135136261620	no	1
Warnings:					
Information:					
2	Issue Fee Payment (PTO-85B)	85.pdf	108437 b609ea9972eda098484ea34e2da2dcc84d84724e	no	1
Warnings:					
Information:					
3	Fee Worksheet (SB06)	fee-info.pdf	30897 d5ba7d1e7200e32b9af15817b1946d2c69092517	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	201814		

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New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

Attorney's Docket No.: 26047-0003011 / 3000-US-0008CON8

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Named Inventor	:	James S. Baldassarre	Art Unit	:	1613
Serial No.	:	14/454,373	Examiner	:	Ernst V. Arnold
Filed	:	August 7, 2014	Confirmation No.	:	3860
			Notice of Allowance Date: November 20, 2014		
Title	:	METHODS FOR IMPROVING THE SAFETY OF TREATING PEDIATRIC PATIENTS WHO ARE CANDIDATES FOR INHALED NITRIC OXIDE TREATMENT			

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REPLY TO NOTICE OF ALLOWANCE

In response to the Notice of Allowance mailed November 20, 2014, enclosed is a completed Part B - Fee(s) Transmittal.

The issue fee in the amount of $480 is being paid with this reply on the Electronic Filing System. Apply that fee and any other necessary charges or credits to Deposit Account 06-1050, referencing the above attorney docket number.

Respectfully submitted,

Date: December 29, 2014

/Janis K. Fraser/
Janis K. Fraser, Ph.D., J.D.
Reg. No. 34,819

Customer Number 94169
Fish & Richardson P.C.
Telephone: (617) 542-5070
Facsimile: (877) 769-7945

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UNITED STATES DEPARTMENT OF COMMERCE
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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
14/454,373	08/07/2014	James S. Baldassarre	26047-0003011

CONFIRMATION NO. 3860

94169
Fish & Richardson PC
P.O.Box 1022
minneapolis, MN 55440

PUBLICATION NOTICE

OC000000072083376

Title:METHODS FOR IMPROVING THE SAFETY OF TREATING PEDIATRIC PATIENTS WHO ARE CANDIDATES FOR INHALED NITRIC OXIDE TREATMENT

Publication No.US-2014-0348955-A1
Publication Date:11/27/2014

NOTICE OF PUBLICATION OF APPLICATION

The above-identified application will be electronically published as a patent application publication pursuant to 37 CFR 1.211, et seq. The patent application publication number and publication date are set forth above.

The publication may be accessed through the USPTO's publically available Searchable Databases via the Internet at www.uspto.gov. The direct link to access the publication is currently http://www.uspto.gov/patft/.

The publication process established by the Office does not provide for mailing a copy of the publication to applicant. A copy of the publication may be obtained from the Office upon payment of the appropriate fee set forth in 37 CFR 1.19(a)(1). Orders for copies of patent application publications are handled by the USPTO's Office of Public Records. The Office of Public Records can be reached by telephone at (703) 308-9726 or (800) 972-6382, by facsimile at (703) 305-8759, by mail addressed to the United States Patent and Trademark Office, Office of Public Records, Alexandria, VA 22313-1450 or via the Internet.

In addition, information on the status of the application, including the mailing date of Office actions and the dates of receipt of correspondence filed in the Office, may also be accessed via the Internet through the Patent Electronic Business Center at www.uspto.gov using the public side of the Patent Application Information and Retrieval (PAIR) system. The direct link to access this status information is currently http://pair.uspto.gov/. Prior to publication, such status information is confidential and may only be obtained by applicant using the private side of PAIR.

Further assistance in electronically accessing the publication, or about PAIR, is available by calling the Patent Electronic Business Center at 1-866-217-9197.

Office of Data Managment, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101

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NOTICE OF ALLOWANCE AND FEE(S) DUE

94169 7590 11/20/2014

Fish & Richardson PC
P.O.Box 1022
minneapolis, MN 55440

EXAMINER
ARNOLD, ERNST V

ART UNIT	PAPER NUMBER
1613	

DATE MAILED: 11/20/2014

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/454,373	08/07/2014	James S. Baldassarre	26047-0003011	3860

TITLE OF INVENTION: METHODS FOR IMPROVING THE SAFETY OF TREATING PEDIATRIC PATIENTS WHO ARE CANDIDATES FOR INHALED NITRIC OXIDE TREATMENT

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	SMALL	$480	$0	$0	$480	02/20/2015

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the ENTITY STATUS shown above. If the ENTITY STATUS is shown as SMALL or MICRO, verify whether entitlement to that entity status still applies.

If the ENTITY STATUS is the same as shown above, pay the TOTAL FEE(S) DUE shown above.

If the ENTITY STATUS is changed from that shown above, on PART B - FEE(S) TRANSMITTAL, complete section number 5 titled "Change in Entity Status (from status indicated above)".

For purposes of this notice, small entity fees are 1/2 the amount of undiscounted fees, and micro entity fees are 1/2 the amount of small entity fees.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed and an extra copy of the form should be submitted. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Utility patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees. It is patentee's responsibility to ensure timely payment of maintenance fees when due.

PTOL-85 (Rev. 02/11)

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: Mail **Mail Stop ISSUE FEE**
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
or Fax (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

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minneapolis, MN 55440

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission
I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO (571) 273-2885, on the date indicated below.

(Depositor's name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/454,373	08/07/2014	James S. Baldassarre	26047-0003011	3860

TITLE OF INVENTION: METHODS FOR IMPROVING THE SAFETY OF TREATING PEDIATRIC PATIENTS WHO ARE CANDIDATES FOR INHALED NITRIC OXIDE TREATMENT

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	SMALL	$480	$0	$0	$480	02/20/2015

EXAMINER	ART UNIT	CLASS-SUBCLASS
ARNOLD, ERNST V	1613	424-718000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).
- ❑ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.
- ❑ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.
1 _____
2 _____
3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ❑ Individual ❑ Corporation or other private group entity ❑ Government

4a. The following fee(s) are submitted:
- ❑ Issue Fee
- ❑ Publication Fee (No small entity discount permitted)
- ❑ Advance Order - # of Copies _____

4b. Payment of Fee(s): **(Please first reapply any previously paid issue fee shown above)**
- ❑ A check is enclosed.
- ❑ Payment by credit card. Form PTO-2038 is attached.
- ❑ The director is hereby authorized to charge the required fee(s), any deficiency, or credits any overpayment, to Deposit Account Number _____ (enclose an extra copy of this form).

5. **Change in Entity Status** (from status indicated above)
- ❑ Applicant certifying micro entity status. See 37 CFR 1.29 — NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.
- ❑ Applicant asserting small entity status. See 37 CFR 1.27 — NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.
- ❑ Applicant changing to regular undiscounted fee status. — NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

PTOL-85 Part B (10-13) Approved for use through 10/31/2013. OMB 0651-0033 U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/454,373	08/07/2014	James S. Baldassarre	26047-0003011	3860

94169 7590 11/20/2014

Fish & Richardson PC
P.O.Box 1022
minneapolis, MN 55440

EXAMINER	
ARNOLD, ERNST V	
ART UNIT	PAPER NUMBER
1613	

DATE MAILED: 11/20/2014

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(Applications filed on or after May 29, 2000)

The Office has discontinued providing a Patent Term Adjustment (PTA) calculation with the Notice of Allowance.

Section 1(h)(2) of the AIA Technical Corrections Act amended 35 U.S.C. 154(b)(3)(B)(i) to eliminate the requirement that the Office provide a patent term adjustment determination with the notice of allowance. See Revisions to Patent Term Adjustment, 78 Fed. Reg. 19416, 19417 (Apr. 1, 2013). Therefore, the Office is no longer providing an initial patent term adjustment determination with the notice of allowance. The Office will continue to provide a patent term adjustment determination with the Issue Notification Letter that is mailed to applicant approximately three weeks prior to the issue date of the patent, and will include the patent term adjustment on the patent. Any request for reconsideration of the patent term adjustment determination (or reinstatement of patent term adjustment) should follow the process outlined in 37 CFR 1.705.

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

OMB Clearance and PRA Burden Statement for PTOL-85 Part B

The Paperwork Reduction Act (PRA) of 1995 requires Federal agencies to obtain Office of Management and Budget approval before requesting most types of information from the public. When OMB approves an agency request to collect information from the public, OMB (i) provides a valid OMB Control Number and expiration date for the agency to display on the instrument that will be used to collect the information and (ii) requires the agency to inform the public about the OMB Control Number's legal significance in accordance with 5 CFR 1320.5(b).

The information collected by PTOL-85 Part B is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450. Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Notice of Allowability	Application No. 14/454,373	Applicant(s) BALDASSARRE, JAMES S.	
	Examiner ERNST V. ARNOLD	Art Unit 1613	AIA (First Inventor to File) Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to *10/31/14*.
   ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on_____.
2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.
3. ☒ The allowed claim(s) is/are *31-60*. As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov .
4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

   Certified copies:

   a) ☐ All b) ☐ Some *c) ☐ None of the:
   1. ☐ Certified copies of the priority documents have been received.
   2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
   3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).
6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☐ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date _____
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
4. ☐ Interview Summary (PTO-413), Paper No./Mail Date _____ .
5. ☐ Examiner's Amendment/Comment
6. ☒ Examiner's Statement of Reasons for Allowance
7. ☐ Other _____.

/ERNST V ARNOLD/
Primary Examiner, Art Unit 1613

The present application is being examined under the pre-AIA first to invent provisions.

DETAILED ACTION

Claims 31-60 are pending and under examination.

Withdrawn rejections:

Applicant's terminal disclaimers and arguments filed 10/31/14 are acknowledged and have been fully considered. The Examiner has re-weighed all the evidence of record. Any rejection and/or objection not specifically addressed below is herein withdrawn.

Terminal Disclaimer

The terminal disclaimers filed on 10/31/14 disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of 14451057 and US Patent No's:

8,795,741; 8,431,163; 8,293,284; and 8,282,966

has been reviewed and is accepted. The terminal disclaimer has been recorded.

Allowable Subject Matter

The following is an examiner's statement of reasons for allowance: the terminal disclaimers are proper and there are no remaining issues.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

Conclusion

Claims 31-60, renumbered as 1-30, are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ERNST V. ARNOLD whose telephone number is (571)272-8509. The examiner can normally be reached on M-F 7:15-4:45.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brian Kwon can be reached on 571-272-0581. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/ERNST V ARNOLD/
Primary Examiner, Art Unit 1613

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14454373	BALDASSARRE, JAMES S.
	Examiner	Art Unit
	ERNST V ARNOLD	1613

CPC- SEARCHED		
Symbol	Date	Examiner

CPC COMBINATION SETS - SEARCHED		
Symbol	Date	Examiner

US CLASSIFICATION SEARCHED			
Class	Subclass	Date	Examiner
424	718 text limited	11/5/14	eva

SEARCH NOTES		
Search Notes	Date	Examiner
inventor/assignee name EAST/PALM	9/8/14	eva
EAST	9/8/14	eva
updated IDS	10/14/14	eva
search update EAST	11/5/14	eva

INTERFERENCE SEARCH			
US Class/ CPC Symbol	US Subclass / CPC Group	Date	Examiner
424	718 text limited	11/5/14	eva

OK to Enter
/EA/
11/5/14

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Named Inventor	:	James S. Baldassarre	Art Unit	:	1613
Serial No.	:	14/454,373	Examiner	:	Ernst V. Arnold
Filed	:	August 7, 2014	Conf. No.	:	3860

Title : METHODS FOR IMPROVING THE SAFETY OF TREATING PEDIATRIC PATIENTS WHO ARE CANDIDATES FOR INHALED NITRIC OXIDE TREATMENT

MAIL STOP AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

REPLY TO FINAL ACTION OF OCTOBER 28, 2014

Please consider the following reply.

EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	0	"14451057"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2014/11/05 08:41
L2	0	424/718.ccls. and ((pulmonary adj hypertension) and (child or pediatric or neonate or neonatal or baby or infant or children) and (inhale or inhaled or breathe or breathable or inhaling) and (nitri adj oxide) and (ventricular with dysfunction)).clm.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2014/11/05 08:43
L5	0	((pulmonary adj hypertension) and (child or pediatric or neonate or neonatal or baby or infant or children) and (inhale or inhaled or breathe or breathable or inhaling) and (nitri adj oxide) and (ventricular with dysfunction)).clm.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2014/11/05 08:44
L6	2	424/718.ccls. and ((pulmonary adj hypertension) and (child or pediatric or neonate or neonatal or baby or infant or children) and (inhale or inhaled or breathe or breathable or inhaling) and (nitric adj oxide) and (ventricular with dysfunction)).clm.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2014/11/05 08:44
L9	3	((pulmonary adj hypertension) and (child or pediatric or neonate or neonatal or baby or infant or children) and (inhale or inhaled or breathe or breathable or inhaling) and (nitric adj oxide) and (ventricular with dysfunction)).clm.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2014/11/05 08:45
S1	2	"8795741".pn.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2014/09/05 08:39
S2	4	"8431163".pn.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2014/09/05 08:39
S3	2	"8293284".pn.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2014/09/05 08:39

S4	2	"8282966".pn.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2014/09/05 08:39
S5	10	((baldassarre.in. or "INO.as") and ((inhaled adj nitric) and (ventricular with dysfunction) and edema).clm.)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2014/09/05 08:42
S6	4	S5 and (discontinuation or discontinuing).clm.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2014/09/05 08:56

EAST Search History (Interference)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L3	0	424/718.ccls. and ((pulmonary adj hypertension) and (child or pediatric or neonate or neonatal or baby or infant or children) and (inhale or inhaled or breathe or breathable or inhaling) and (nitri adj oxide) and (ventricular with dysfunction)).clm.	US-PGPUB; USPAT; UPAD	OR	ON	2014/11/05 08:43
L4	0	((pulmonary adj hypertension) and (child or pediatric or neonate or neonatal or baby or infant or children) and (inhale or inhaled or breathe or breathable or inhaling) and (nitri adj oxide) and (ventricular with dysfunction)).clm.	US-PGPUB; USPAT; UPAD	OR	ON	2014/11/05 08:44
L7	2	424/718.ccls. and ((pulmonary adj hypertension) and (child or pediatric or neonate or neonatal or baby or infant or children) and (inhale or inhaled or breathe or breathable or inhaling) and (nitric adj oxide) and (ventricular with dysfunction)).clm.	US-PGPUB; USPAT; UPAD	OR	ON	2014/11/05 08:44
L8	4	((pulmonary adj hypertension) and (child or pediatric or neonate or neonatal or baby or infant or children) and (inhale or inhaled or breathe or breathable or inhaling) and (nitric adj oxide) and (ventricular with dysfunction)).clm.	US-PGPUB; USPAT; UPAD	OR	ON	2014/11/05 08:44

11/5/2014 9:42:39 AM
C:\Users\earnold\Documents\EAST\Workspaces\14451057.wsp

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14454373	BALDASSARRE, JAMES S.
	Examiner	**Art Unit**
	ERNST V ARNOLD	1613

CPC						
Symbol					**Type**	**Version**
A61K		33	/	00	F	2013-01-01
A61K		45	/	06	I	2013-01-01
A61M		16	/	0057	I	2013-01-01
A61M		16	/	12	I	2013-01-01
A61M		16	/	104	I	2013-01-01
A61B		8	/	0883	I	2013-01-01
A61B		5	/	0205	I	2013-01-01
A61B		5	/	4839	I	2013-01-01
A61B		5	/	7278	I	2013-01-01
A61B		5	/	7275	I	2013-01-01
A61B		5	/	08	A	2013-01-01
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CPC Combination Sets							
Symbol					**Type**	**Set**	**Ranking**	**Version**
			/					
			/					

NONE		**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	30	
/ERNST V ARNOLD/ Primary Examiner.Art Unit 1613	11/5/14	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	none

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14454373	BALDASSARRE, JAMES S.
	Examiner	**Art Unit**
	ERNST V ARNOLD	1613

US ORIGINAL CLASSIFICATION		INTERNATIONAL CLASSIFICATION										
CLASS	SUBCLASS	CLAIMED					NON-CLAIMED					
424	718	A	6	1	K	33 / 00 (2006.01.01)						
CROSS REFERENCE(S)												
CLASS	SUBCLASS (ONE SUBCLASS PER BLOCK)											

NONE		Total Claims Allowed:	
(Assistant Examiner)	(Date)	30	
/ERNST V ARNOLD/ Primary Examiner.Art Unit 1613	11/5/14	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	none

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14454373	BALDASSARRE, JAMES S.
	Examiner	**Art Unit**
	ERNST V ARNOLD	1613

☒ Claims renumbered in the same order as presented by applicant ☐ CPA ☒ T.D. ☐ R.1.47

Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original

NONE (Assistant Examiner)	(Date)	**Total Claims Allowed:** 30	
/ERNST V ARNOLD/ Primary Examiner.Art Unit 1613 (Primary Examiner)	11/5/14 (Date)	O.G. Print Claim(s) 1	O.G. Print Figure none

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14454373	BALDASSARRE, JAMES S.
	Examiner	**Art Unit**
	ERNST V ARNOLD	1613

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

☒ Claims renumbered in the same order as presented by applicant ☐ CPA ☒ T.D. ☐ R.1.47

CLAIM		DATE								
Final	Original	11/05/2014								
	1	-								
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	36	=								

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14454373	BALDASSARRE, JAMES S.
	Examiner	**Art Unit**
	ERNST V ARNOLD	1613

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

☒ Claims renumbered in the same order as presented by applicant ☐ CPA ☒ T.D. ☐ R.1.47

CLAIM		DATE								
Final	Original	11/05/2014								
	37	=								
	38	=								
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	40	=								
	41	=								
	42	=								
	43	=								
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UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

BIB DATA SHEET

CONFIRMATION NO. 3860

SERIAL NUMBER	FILING or 371(c) DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
14/454,373	08/07/2014 RULE	424	1613	26047-0003011

APPLICANTS

INO Therapeutics LLC, Hampton, NJ, Assignee (with 37 CFR 1.172 Interest);

INVENTORS

James S. Baldassarre, Doylestown, PA;

**** CONTINUING DATA ***************************

This application is a CON of 14/451,057 08/04/2014
which is a CON of 13/683,417 11/21/2012 PAT 8795741
which is a CON of 12/820,866 06/22/2010 ABN
which is a CON of 12/494,598 06/30/2009 ABN
and said 13/683,417 11/21/2012
is a CON of 13/651,660 10/15/2012 PAT 8431163
which is a CON of 12/821,041 06/22/2010 PAT 8293284
which is a CON of 12/494,598 06/30/2009 ABN
and said 14/451,057 08/04/2014
is a DIV of 13/683,444 11/21/2012
which is a DIV of 12/820,866 06/22/2010 ABN
which is a CON of 12/494,598 06/30/2009 ABN
and said 13/683,444 11/21/2012
is a DIV of 13/651,660 10/15/2012 PAT 8431163
which is a CON of 12/821,041 06/22/2010 PAT 8293284
which is a CON of 12/494,598 06/30/2009 ABN
This application 14/454,373 08/07/2014
is a DIV of 13/683,444 11/21/2012
which is a DIV of 12/820,866 06/22/2010 ABN
which is a CON of 12/494,598 06/30/2009 ABN
and said 13/683,444 11/21/2012
is a DIV of 13/651,660 10/15/2012 PAT 8431163
which is a CON of 12/821,041 06/22/2010 PAT 8293284
which is a CON of 12/494,598 06/30/2009 ABN

**** FOREIGN APPLICATIONS ***************************

**** IF REQUIRED, FOREIGN FILING LICENSE GRANTED **** ** SMALL ENTITY **
08/15/2014

Foreign Priority claimed ☐ Yes ☑ No 35 USC 119(a-d) conditions met ☐ Yes ☑ No Verified and Acknowledged /ERNST V ARNOLD/ Examiner's Signature	☐ Met after Allowance Initials	STATE OR COUNTRY	SHEETS DRAWINGS	TOTAL CLAIMS	INDEPENDENT CLAIMS
		PA	0	30	4

ADDRESS

Fish & Richardson PC
P.O.Box 1022
minneapolis, MN 55440
UNITED STATES

TITLE		
Methods for improving the safety of treating pediatric patients who are candidates for inhaled nitric oxide treatment		
FILING FEE RECEIVED 1340	FEES: Authority has been given in Paper No._____ to charge/credit DEPOSIT ACCOUNT No._____ for following:	❑ All Fees ❑ 1.16 Fees (Filing) ❑ 1.17 Fees (Processing Ext. of time) ❑ 1.18 Fees (Issue) ❑ Other _____ ❑ Credit

Application Number	Application/Control No.	Applicant(s)/Patent under Reexamination	
	14/454,373	BALDASSARRE, JAMES S.	

Document Code - DISQ	Internal Document – DO NOT MAIL

TERMINAL DISCLAIMER	☒ APPROVED	☐ DISAPPROVED
Date Filed : 10/31/14	This patent is subject to a Terminal Disclaimer	

Approved/Disapproved by:

ANDRE ROBINSON

5 TDS WERE APPRVD.

PTO/AIA/26 (04-13)
Approved for use through 04/30/2013. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

TERMINAL DISCLAIMER TO OBVIATE A DOUBLE PATENTING REJECTION OVER A "PRIOR" PATENT	Docket Number (Optional) 26047-0003011

In re Application of: INO Therapeutics LLC

Application No.: 14/454,373

Filed: August 7, 2014

For: METHODS FOR IMPROVING THE SAFETY OF TREATING PEDIATRIC PATIENTS WHO ARE CANDIDATES FOR INHALED NITRIC OXIDE TREATMENT

The applicant, INO Therapeutics LLC, owner of 100 percent interest in the instant application, hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application which would extend beyond the expiration date of the full statutory term of any of **prior patent** Nos. 8,795,741; 8,431,163; 8,293,284; and 8,282,966 as the term of said **prior patent** is presently shortened by any terminal disclaimer. The applicant hereby agrees that any patent so granted on the instant application shall be enforceable only for any during such period that it and each of the **prior patents** are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors or assigns.

In making the above disclaimer, the applicant does not disclaim the terminal part of the term of any patent granted on the instant application that would extend to the expiration date of the full statutory term of each of the **prior patents**, "as the term of said **prior patent** is presently shortened by any terminal disclaimer," in the event that said **prior patent** later:

expires for failure to pay a maintenance fee;
is held unenforceable;
is found invalid by a court of competent jurisdiction;
is statutorily disclaimed in whole or terminally disclaimed under 37 CFR 1.321;
has all claims canceled by a reexamination certificate;
is reissued; or
is in any manner terminated prior to the expiration of its full statutory term as presently shortened by any terminal disclaimer.

Check either box 1 or 2 below, if appropriate.

1. ☐ The undersigned is the applicant. If the applicant is an assignee, the undersigned is authorized to act on behalf of the assignee.

I hereby acknowledge that any willful false statements made are punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than five (5) years, or both.

2. ☒ The undersigned is an attorney or agent of record. Reg. No. 34,819

/Janis K. Fraser/ — Signature
October 30, 2014 — Date

Janis K. Fraser, Ph.D., J.D. — Typed or printed name

Attorney — Title
(617) 542-5070 — Telephone Number

☒ Terminal disclaimer fee under 37 CFR 1.20(d) was previously paid.

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Named Inventor	:	James S. Baldassarre	Art Unit	:	1613
Serial No.	:	14/454,373	Examiner	:	Ernst V. Arnold
Filed	:	August 7, 2014	Conf. No.	:	3860
Title	:	METHODS FOR IMPROVING THE SAFETY OF TREATING PEDIATRIC PATIENTS WHO ARE CANDIDATES FOR INHALED NITRIC OXIDE TREATMENT			

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

REQUEST FOR REFUND

On October 14, 2014, Applicant filed a terminal disclaimer in the present case and paid $800 in terminal disclaimer fees, because there were five patent/applications over which the present application was being terminally disclaimed (5 x $160 = $800). The terminal disclaimer was rejected on formal grounds, so is being resubmitted by applicant as two separate filings. USPTO official Lawana Hixon informed applicant on October 30, 2014, that the required $160 terminal disclaimer fee is per form and not per patent/application being disclaimed. Because applicant is submitting 2 forms (Form AIA/25 for a pending reference application and Form AIA/26 for the four prior patents), the total terminal disclaimer fee should be $320 (2 x $160). According to Ms. Hixon, applicant will be due a refund for the difference ($800 - $320 = $480 to be refunded).

Accordingly, applicants respectfully request that the overcharge amount of $480 be refunded to Fish & Richardson's Deposit Account No. 06-1050 as a credit, referencing the above attorney-docket number.

Respectfully submitted,

Date: October 30, 2014

/Janis K. Fraser/
Janis K. Fraser, Ph.D., J.D.
Reg. No. 34,819

Customer Number 94169
Fish & Richardson P.C.
Telephone: (617) 542-5070
Facsimile: (877) 769-7945

23312056.doc

Electronic Acknowledgement Receipt

EFS ID:	20575188
Application Number:	14454373
International Application Number:	
Confirmation Number:	3860
Title of Invention:	Methods for improving the safety of treating pediatric patients who are candidates for inhaled nitric oxide treatment
First Named Inventor/Applicant Name:	James S. Baldassarre
Customer Number:	94169
Filer:	Janis K. Fraser/Christine Grace
Filer Authorized By:	Janis K. Fraser
Attorney Docket Number:	26047-0003011
Receipt Date:	31-OCT-2014
Filing Date:	07-AUG-2014
Time Stamp:	14:12:18
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Response After Final Action	Response.pdf	64092 2a65c91aee27c1e22c8f233a12ac123b0b3358da	no	2

Warnings:	
Information:	

2	Terminal Disclaimer Filed	TD1.pdf	112114 806c0ac09647ab395d7d5fe843dfe7416b2cf9eb	no	1
Warnings:					
Information:					
3	Terminal Disclaimer Filed	TD2.pdf	112068 1258f811dcfbc2ea80fc14223f70efb67e145af2	no	1
Warnings:					
Information:					
4	Refund Request	Refund.pdf	48205 303560b3f72a4478d0bd2f17099e9845c2fb60f3	no	1
Warnings:					
Information:					
		Total Files Size (in bytes):	336479		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

<u>New Applications Under 35 U.S.C. 111</u>
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

<u>National Stage of an International Application under 35 U.S.C. 371</u>
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

<u>New International Application Filed with the USPTO as a Receiving Office</u>
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PTO/AIA/25 (04-13)
Approved for use through 04/30/2013. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

TERMINAL DISCLAIMER TO OBVIATE A PROVISIONAL DOUBLE PATENTING REJECTION OVER A PENDING "REFERENCE" APPLICATION	Docket Number (Optional) 26047-0003011

In re Application of: INO Therapeutics LLC

Application No.: 14/454,373

Filed: August 7, 2014

For: METHODS FOR IMPROVING THE SAFETY OF TREATING PEDIATRIC PATIENTS WHO ARE CANDIDATES FOR INHALED NITRIC OXIDE TREATMENT

The applicant, INO Therapeutics LLC, owner of 100 percent interest in the instant application, hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application which would extend beyond the expiration date of the full statutory term of any patent granted on pending **reference** Application Number 14/451,057, filed August 4, 2014, as the term of any patent granted on said **reference** application may be shortened by any terminal disclaimer filed prior to the grant of any patent on the pending **reference** application. The applicant hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and any patent granted on the **reference** application are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors or assigns.

In making the above disclaimer, the applicant does not disclaim the terminal part of any patent granted on the instant application that would extend to the expiration date of the full statutory term of any patent granted on said **reference** application, "as the term of any patent granted on said **reference** application may be shortened by any terminal disclaimer filed prior to the grant of any patent on the pending **reference** application," in the event that: any such patent granted on the pending **reference** application expires for failure to pay a maintenance fee, is held unenforceable, is found invalid by a court of competent jurisdiction, is statutorily disclaimed in whole or terminally disclaimed under 37 CFR 1.321, has all claims canceled by a reexamination certificate, is reissued, or is in any manner terminated prior to the expiration of its full statutory term as shortened by any terminal disclaimer filed prior to its grant.

Check either box 1 or 2 below, if appropriate.

1. ☐ The undersigned is the applicant. If the applicant is an assignee, the undersigned is authorized to act on behalf of the assignee.

I hereby acknowledge that any willful false statements made are punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than five (5) years, or both.

2. ☒ The undersigned is an attorney or agent of record. Reg. No. 34,819

/Janis K. Fraser/ — Signature
October 30, 2014 — Date

Janis K. Fraser, Ph.D., J.D. — Typed or printed name

Attorney — Title
(617) 542-5070 — Telephone Number

☒ Terminal disclaimer fee under 37 CFR 1.20(d) was previously paid.

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Named Inventor	:	James S. Baldassarre	Art Unit	:	1613
Serial No.	:	14/454,373	Examiner	:	Ernst V. Arnold
Filed	:	August 7, 2014	Conf. No.	:	3860

Title : METHODS FOR IMPROVING THE SAFETY OF TREATING PEDIATRIC PATIENTS WHO ARE CANDIDATES FOR INHALED NITRIC OXIDE TREATMENT

MAIL STOP AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

REPLY TO FINAL ACTION OF OCTOBER 28, 2014

Please consider the following reply.

REMARKS

No amendments are proposed.

Claims 31-60 remain rejected for nonstatutory double patenting, as allegedly being unpatentable over:

1. Claims 1-44 of U.S. Patent No. 8795741;
2. Claims 1-25 of U.S. Patent No. 8431163;
3. Claims 1-29 of U.S. Patent No. 8282966;
4. Claims 1-30 of U.S. Patent No. 8293284; and
5. Claims 31-60 of earlier filed U.S. Application 14451057.

This is the same rejection as set out in the Office action dated September 12, 2014. On October 14, 2014, Applicant responded to that Office action by submitting a terminal disclaimer intended to overcome the rejection. As noted in the present Office action, that terminal disclaimer was rejected on various formal grounds. While disagreeing that the original terminal disclaimer was in any way informal, applicant submits with this Reply two new terminal disclaimers that address the issues raised by the Office. It is believed that the new terminal disclaimers are sufficient to overcome the rejection. Accordingly, allowance of the claims is respectfully requested.

Applicant understands that the previously-paid terminal disclaimer fee will be applied to the terminal disclaimers filed with this Reply. If that is incorrect, apply any necessary fees, and any credits, to Deposit Account 06-1050, referencing the above attorney docket number.

Respectfully submitted,

Date: October 30, 2014

/Janis K. Fraser/
Janis K. Fraser, Ph.D., J.D.
Reg. No. 34,819

Customer Number 94169
Fish & Richardson P.C.
Telephone: (617) 542-5070
Facsimile: (877) 769-7945

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UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/454,373	08/07/2014	James S. Baldassarre	26047-0003011	3860

94169 7590 10/28/2014

Fish & Richardson PC
P.O.Box 1022
minneapolis, MN 55440

EXAMINER	
ARNOLD, ERNST V	
ART UNIT	PAPER NUMBER
1613	
MAIL DATE	DELIVERY MODE
10/28/2014	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 14/454,373	Applicant(s) BALDASSARRE, JAMES S.	
	Examiner ERNST V. ARNOLD	Art Unit 1613	AIA (First Inventor to File) Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10/14/14*.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5)☒ Claim(s) *31-60* is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *31-60* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)

2) ☒ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date *10/14/14*.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

4) ☐ Other: _____.

The present application is being examined under the pre-AIA first to invent provisions.

DETAILED ACTION

Claims 1-30 have been cancelled. Claims 31-60 are new and pending.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on 10/14/14 was filed after the Action filed 9/12/14. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statements are being considered by the examiner.

Withdrawn rejections:

Applicant's Declaration under 37 CFR 1.131, amendments and arguments filed 10/14/14 are acknowledged and have been fully considered. The Examiner has re-weighed all the evidence of record. Any rejection and/or objection not specifically addressed below is herein withdrawn.

The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set of rejections and/or objections presently being applied to the instant application.

Terminal Disclaimer

The terminal disclaimer filed on 10/14/14 disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of the cited documents has been reviewed and is NOT accepted for the following reasons:

Approved/Disapproved by:

Td disapproved.

The filing date for pending reference applications are missing.

All cases are missing percentage.

Please use PTO/AIA/25 form. (Pending Reference)-after September 16, 2012 (optional)

Please use PTO/AIA/26 form. (Prior Patent)-after September 16, 2012 (optional)

Please separate pending reference applications from prior patent applications.

Also resubmit Tds with these papers. NO Fee is required unless filing more than one TD.

Lawana Hixon

Until these issues are corrected, the double patenting rejections remain in effect.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory double patenting rejection is appropriate where the claims at issue are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d

1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the reference application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement. A terminal disclaimer must be signed in compliance with 37 CFR 1.321(b).

The USPTO internet Web site contains terminal disclaimer forms which may be used. Please visit http://www.uspto.gov/forms/. The filing date of the application will determine what form should be used. A web-based eTerminal Disclaimer may be filled out completely online using web-screens. An eTerminal Disclaimer that meets all requirements is auto-processed and approved immediately upon submission. For more information about eTerminal Disclaimers, refer to http://www.uspto.gov/patents/process/file/efs/guidance/eTD-info-I.jsp.

Claims 31-60 are rejected on the ground of nonstatutory double patenting as being unpatentable over:

1. Claims 1-44 of U.S. Patent No. 8795741;
2. Claims 1-25 of U.S. Patent No. 8431163;
3. Claims 1-29 of U.S. Patent No. 8282966;

4. Claims 1-30 of U.S. Patent No. 8293284; and

5. Claims 31-60 of earlier filed U.S. Application 14451057.

Although the claims at issue are not identical, they are not patentably distinct from each other because all the patents and patent application are directed to methods of administering 20 ppm inhaled nitric oxide to children/neonates to reduce the risk of pulmonary edema, and thus improve the safety of treating hypoxic respiratory failure in neoates/pediatric patients, and excluding children from treatment that have left ventricular dysfunction. Treatment for 14 days, administration until hypoxia has resolved and further therapeutic treatment of select patients by mechanical ventilation, vasodilators, i.v. fluids and bicarbonate therapy is merely judicious selection of known therapies by the ordinary artisan. Discontinuation of therapy is also a decision performed by the ordinary artisan and an obvious choice.

Consequently, the ordinary artisan would have recognized the obvious variation of the instant subject matter over the patented subject matter.

Response to Arguments:

Applicant's terminal disclaimer has not been approved. Therefore the rejections are maintained. As to the statement concerning the claimed scope, one need only read the cited claims to see the details of the claimed subject matter and their obvious overlap. This is confirmed by the extensive number of terminal disclaimers also filed in prosecution history of these related applications. Thus, while the description above may be general, the rejection is nevertheless appropriate.

Conclusion

No claims are allowed at this time.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ERNST V. ARNOLD whose telephone number is (571)272-8509. The examiner can normally be reached on M-F 7:15-4:45.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brian Kwon can be reached on 571-272-0581. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/ERNST V ARNOLD/
Primary Examiner, Art Unit 1613

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14454373	BALDASSARRE, JAMES S.
	Examiner	Art Unit
	ERNST V ARNOLD	1613

CPC- SEARCHED		
Symbol	Date	Examiner

CPC COMBINATION SETS - SEARCHED		
Symbol	Date	Examiner

US CLASSIFICATION SEARCHED			
Class	Subclass	Date	Examiner

SEARCH NOTES		
Search Notes	Date	Examiner
inventor/assignee name EAST/PALM	9/8/14	eva
EAST	9/8/14	eva
updated IDS	10/14/14	eva

INTERFERENCE SEARCH			
US Class/ CPC Symbol	US Subclass / CPC Group	Date	Examiner

Receipt date: 10/14/2014 14454373 - GAU: 1613

Doc code: IDS PTO/SB/08a (01-10)

Doc description: Information Disclosure Statement (IDS) Filed

Approved for use through 07/31/2012. OMB 0651-0031

U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99)**		
	Application Number	14454373
	Filing Date	2014-08-07
	First Named Inventor	Baldassarre
	Art Unit	1613
	Examiner Name	
	Attorney Docket Number	26047-0003011

U.S.PATENTS Remove

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1					

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Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
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Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2] i	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]
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Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]

EFS Web 2.1.17 ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /E.A./

Receipt date: 10/14/2014	Application Number	14454373 14454373 - GAU: 1613
INFORMATION DISCLOSURE STATEMENT BY APPLICANT	Filing Date	2014-08-07
	First Named Inventor	Baldassarre
(Not for submission under 37 CFR 1.99)	Art Unit	1613
	Examiner Name	
	Attorney Docket Number	26047-0003011

	1	U.S. Examiner Ernst V. Arnold, Office Action in U.S. Serial No. 13/683,236, mailed April 24, 2013 (17 pages)	☐
	2	Fish & Richardson, P.C., Amendment in Reply to Action in U.S. Serial No. 13/683,236, filed December 23, 2013 (309 pages)	☐

If you wish to add additional non-patent literature document citation information please click the Add button Add

EXAMINER SIGNATURE

Examiner Signature	/Ernst Arnold/	Date Considered	10/28/2014

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /E.A./

Receipt date: 10/14/2014	Application Number	14454373	14454373 - GAU: 1613
INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99)**	Filing Date	2014-08-07	
	First Named Inventor	Baldassarre	
	Art Unit	1613	
	Examiner Name		
	Attorney Docket Number	26047-0003011	

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☐ See attached certification statement.

☒ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Janis K. Fraser/	Date (YYYY-MM-DD)	2014-10-14
Name/Print	Janis K. Fraser	Registration Number	34819

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /E.A./

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these record s.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /E.A./

Application Number	Application/Control No.	Applicant(s)/Patent under Reexamination	
	14/454,373	BALDASSARRE, JAMES S.	

Document Code - DISQ	Internal Document – DO NOT MAIL

TERMINAL DISCLAIMER	☐ APPROVED	☒ DISAPPROVED
Date Filed : 10/14/14	**This patent is subject to a Terminal Disclaimer**	

Approved/Disapproved by:

Td disapproved.

The filing date for pending reference applications are missing.

All cases are missing percentage.

Please use PTO/AIA/25 form. (Pending Reference)-after September 16, 2012 (opitional)

Please use PTO/AIA/26 form. (Prior Patent)-after September 16, 2012 (opitional)

Please separate pending reference applications from prior patent applications.

Also resubmit Tds with these papers. NO Fee is required unless filing more than one TD.

Lawana Hixon

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	: INO Therapeutics LLC	Art Unit	: 1613
Serial No.	: 14/454,373	Examiner	: Ernst V. Arnold
Filed	: August 07, 2014	Conf. No.	: 3860
Title	: METHODS FOR IMPROVING THE SAFETY OF TREATING PEDIATRIC PATIENTS WHO ARE CANDIDATES FOR INHALED NITRIC OXIDE TREATMENT		

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

REPLY TO ACTION OF SEPTEMBER 12, 2014

No amendments are proposed.

Double patenting

The action of September 12, 2014, rejects the claims for alleged obviousness-type double patenting over the claims of four patents and one application:

US Patent No. 8795741;

US Patent No. 8431163;

US Patent No. 8282966;

US Patent No. 8393284; and

US Application serial no. 14/451057.

Submitted with this reply is a terminal disclaimer believed adequate to overcome the rejection.

As the double patenting rejections were the only rejections asserted in the Office action, applicant respectfully requests allowance of the present application.

Statement regarding claim scope

Applicant notes the statement on page 4 of the Office action that purports to provide a general description of the claims of the above-listed patents and application. While many or all of the limitations described in that statement are indeed present in at least some of

the claims of those patents and application, such a general statement could not begin to address all of the details of all of the claims of all of the patents.

Declaration under 37 CFR 1.131

Also submitted with this reply is a Declaration Under 37 C.F.R. § 1.131, signed by the inventor, James S. Baldassarre, M.D.. Although not prompted by anything in the present Office action, the Declaration is being filed to ensure that the record is clear that the present claims are entitled to a date of invention that is prior to July 14, 2008. That date is the apparent publication date of a document entitled "Autorisation De Mise Sur Le Marche for VasoKINOX 450 ppm mole/mole" issued by the Belgian Federal Agency for Drug and Medical Products (BE 329336), which was cited in a rejection in a related application, U.S. Application Serial No. 13/683,236, in an Office action dated April 24, 2013. A copy of that Office action from the related application, and a copy of applicant's response to it, are submitted in an Information Disclosure Statement that is being filed with this reply. The VasoKINOX document itself was made of record in the present case in an Information Disclosure Statement filed August 25, 2014.

The fees of $800 for the terminal disclaimers and $90 for the Information Disclosure Statement are being paid on the Electronic Filing System (EFS) by way of Deposit Account authorization. Apply any necessary charges or credits to Deposit Account 06-1050, referencing the above attorney docket number.

Respectfully submitted,

Date: October 14, 2014

/Janis K. Fraser/
Janis K. Fraser, Ph.D., J.D.
Reg. No. 34,819

Customer Number 94169
Fish & Richardson P.C.
Telephone: 617/542-5070
Facsimile: 617/542-8906

1210899o.docx

Doc code: IDS
Doc description: Information Disclosure Statement (IDS) Filed

PTO/SB/08a (01-10)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99)**		
	Application Number	14454373
	Filing Date	2014-08-07
	First Named Inventor	Baldassarre
	Art Unit	1613
	Examiner Name	
	Attorney Docket Number	26047-0003011

U.S.PATENTS Remove

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
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If you wish to add additional U.S. Patent citation information please click the Add button. Add

U.S.PATENT APPLICATION PUBLICATIONS Remove

Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1					

If you wish to add additional U.S. Published Application citation information please click the Add button. Add

FOREIGN PATENT DOCUMENTS Remove

Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2] i	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]
	1							☐

If you wish to add additional Foreign Patent Document citation information please click the Add button Add

NON-PATENT LITERATURE DOCUMENTS Remove

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	14454373
	Filing Date	2014-08-07
	First Named Inventor	Baldassarre
	Art Unit	1613
	Examiner Name	
	Attorney Docket Number	26047-0003011

	1	U.S. Examiner Ernst V. Arnold, Office Action in U.S. Serial No. 13/683,236, mailed April 24, 2013 (17 pages)	☐
	2	Fish & Richardson, P.C., Amendment in Reply to Action in U.S. Serial No. 13/683,236, filed December 23, 2013 (309 pages)	☐

If you wish to add additional non-patent literature document citation information please click the Add button Add

EXAMINER SIGNATURE

Examiner Signature		Date Considered	

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	Application Number	14454373
	Filing Date	2014-08-07
	First Named Inventor	Baldassarre
	Art Unit	1613
	Examiner Name	
	Attorney Docket Number	26047-0003011

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OR

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☐ See attached certification statement.

☒ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Janis K. Fraser/	Date (YYYY-MM-DD)	2014-10-14
Name/Print	Janis K. Fraser	Registration Number	34819

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Electronic Patent Application Fee Transmittal

Application Number:	14454373
Filing Date:	07-Aug-2014
Title of Invention:	Methods for improving the safety of treating pediatric patients who are candidates for inhaled nitric oxide treatment
First Named Inventor/Applicant Name:	James S. Baldassarre
Filer:	Janis K. Fraser/Christine Grace
Attorney Docket Number:	26047-0003011

Filed as Small Entity

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
Submission- Information Disclosure Stmt	2806	1	90	90
Statutory or Terminal Disclaimer	1814	5	160	800
		Total in USD ($)		**890**

Electronic Acknowledgement Receipt

EFS ID:	20412657
Application Number:	14454373
International Application Number:	
Confirmation Number:	3860
Title of Invention:	Methods for improving the safety of treating pediatric patients who are candidates for inhaled nitric oxide treatment
First Named Inventor/Applicant Name:	James S. Baldassarre
Customer Number:	94169
Filer:	Janis K. Fraser/Christine Grace
Filer Authorized By:	Janis K. Fraser
Attorney Docket Number:	26047-0003011
Receipt Date:	14-OCT-2014
Filing Date:	07-AUG-2014
Time Stamp:	16:48:41
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$890
RAM confirmation Number	3749
Deposit Account	061050
Authorized User	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)

1	Amendment/Req. Reconsideration-After Non-Final Reject	Response.pdf	72256 2ac3472aa06aeaebf10371feae972e7fafe94b25	no	2
Warnings:					
Information:					
2	Terminal Disclaimer Filed	TD.pdf	79835 2c2fdf9952cacdfdf302e8a0d9e1d93b345ecb94	no	4
Warnings:					
Information:					
3	Affidavit-Rule 131-pre-AIA (FTI) ONLY	131.pdf	7711697 bba3089b10e894b54c9be08e3c9bc09e7fd10f0b	no	219
Warnings:					
Information:					
4	Information Disclosure Statement (IDS) Form (SB08)	SB08.pdf	611965 8a80e10203144575f32bcfc8a8a570b4a7637b1e	no	4
Warnings:					
Information:					
A U.S. Patent Number Citation or a U.S. Publication Number Citation is required in the Information Disclosure Statement (IDS) form for autoloading of data into USPTO systems. You may remove the form to add the required data in order to correct the Informational Message if you are citing U.S. References. If you chose not to include U.S. References, the image of the form will be processed and be made available within the Image File Wrapper (IFW) system. However, no data will be extracted from this form. Any additional data such as Foreign Patent Documents or Non Patent Literature will be manually reviewed and keyed into USPTO systems.					
5	Non Patent Literature	OA.pdf	705327 6ddb6f50f2dda955dbdead014fb1ebc7877b15c0	no	17
Warnings:					
Information:					
6	Non Patent Literature	Rep.pdf	7618373 5cdb83b1f5eb4af0762d157c6fe5cab5b6def6a9	no	309
Warnings:					
Information:					
7	Fee Worksheet (SB06)	fee-info.pdf	32016 d36f6391ac5aadda5d9f916f7f27631e6e08d302	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	16831469		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Named Inventor	:	James S. Baldassarre	Art Unit	:	1613
Serial No.	:	14/454,373	Examiner	:	Ernst V. Arnold
Filed	:	August 7, 2014	Conf. No.	:	3860
Title	:	METHODS FOR IMPROVING THE SAFETY OF TREATING PEDIATRIC PATIENTS WHO ARE CANDIDATES FOR INHALED NITRIC OXIDE TREATMENT			

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

TERMINAL DISCLAIMER UNDER 37 C.F.R. §§ 3.73(b) AND 1.321(c)

Pursuant to 37 C.F.R. § 3.73(b), INO THERAPEUTICS LLC, a corporation, certifies that it is the assignee of the entire right, title, and interest in the present application (a 100% ownership interest) by virtue of a chain of title from the inventor of the present patent application to the current assignee, as shown below:

1. From James S. Baldassarre[1] to Ikaria Holdings, Inc. The document was recorded in the Patent and Trademark Office at Reel 033807, Frame 0729.

2. From Ikaria Holdings, Inc. to Ikaria, Inc. The document was recorded in the Patent and Trademark Office at Reel 033807, Frame 0903.

3. From Ikaria, Inc. to INO Therapeutics LLC. The document was recorded in the Patent and Trademark Office at Reel 033808, Frame 0062, and a corrected version was recorded at Reel 033887, Frame 0427 (to correct the spelling of the Assignee's name).

[1] This assignment was originally filed in a predecessor application (USSN 12/494,598). That predecessor application originally named two co-inventors, James S. Baldassarre and Ralf Rosskamp. Inventorship for this family of cases has since been corrected to name only James S. Baldassarre as sole inventor. The present application was filed naming only Dr. Baldassarre as sole inventor. The naming of Dr. Rosskamp on the assignment filed in this case is thus an artifact of the assignment's history and does not alter the fact that he is not a co-inventor.

To the best of undersigned's knowledge and belief, title is in the assignee identified above.

The undersigned is empowered to act on behalf of the assignee.

Pursuant to 37 C.F.R. § 1.321(c), and to obviate a double patenting rejection, the assignee identified above hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application that would extend beyond the expiration date of the full statutory term of any of the four patents listed in the attached Exhibit A, or of any U.S. patent that issues from the patent application listed in Exhibit A (together, the four listed patents and any U.S. patent that issues from the listed application are referred to as the "Exhibit A Patents"). The assignee hereby agrees that any patent granted on the instant application shall be enforceable only for and during such period that it is commonly owned with each of the Exhibit A Patents and the patent application listed in Exhibit A.

The assignee identified above does not disclaim any terminal part of any patent granted on the present application that would extend to the expiration date of the full statutory term of any of the Exhibit A Patents in the event that any of the Exhibit A Patents later: expires for failure to pay a maintenance fee, is held unenforceable, is found invalid by a court of competent jurisdiction, is statutorily disclaimed in whole or terminally disclaimed under 37 C.F.R. § 1.321, has all claims cancelled by a reexamination certificate, is reissued, or is otherwise terminated prior to expiration of its full statutory term. The full statutory term of any U.S. patent includes any term adjustment as defined in 35 U.S.C. § 154 and § 173. Assignee herein does not disclaim or otherwise affect any part of the Exhibit A Patents or of the patent application listed in Exhibit A.

This disclaimer runs with any patent granted on the present application and is binding upon the grantee, its successors or assigns.

The fees totaling $800 for five terminal disclaimers, as required by 37 C.F.R. § 1.20(d), are being paid on the Electronic Filing System. Apply those fees and any other necessary charges or credits to Deposit Account 06-1050, referencing the above attorney docket number.

Respectfully submitted,

Date: October 14, 2014

/Janis K. Fraser/
Janis K. Fraser, Ph.D., J.D.
Reg. No. 34,819

Fish & Richardson P.C.
Customer No. 94169
Telephone: (617) 542-5070
Facsimile: (877) 769-7945

23262675.doc

EXHIBIT A

1. U.S. Patent No. 8,795,741
2. U.S. Patent No. 8,431,163
3. U.S. Patent No. 8,282,966
4. U.S. Patent No. 8,293,284
5. U.S. application serial no. 14/451,057

Attorney Docket No.: 26047-0003011
Client Ref. No.: 3000-US-0008CON8

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : James S. Baldassarre Conf. No. : 3860
Serial No. : 14/454,373
Filed : August 7, 2014
Title : METHODS FOR IMPROVING THE SAFETY OF TREATING PEDIATRIC PATIENTS WHO ARE CANDIDATES FOR INHALED NITRIC OXIDE TREATMENT

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION UNDER 37 C.F.R. § 1.131

I, James S. Baldassarre, M.D., declare as follows:

1. I have over 25 years of experience as a physician and over 20 years of experience directing clinical research in the pharmaceutical industry. I was employed by INO Therapeutics LLC ("INOT"), the current assignee of U.S. Patent Application No. 14/454,373 (as captioned above, "the present application"), and/or Ikaria, Inc., the parent company of INOT, from October 2003 until September 2013. I currently serve as a paid consultant of INOT and retain an equity interest in the company.

2. I am the inventor of the subject matter claimed in the present application. This application is a continuation of U.S. Serial No. 14/451,057, filed August 4, 2014, which is a continuation of U.S. Serial No. 13/683,417 (now U.S. Patent No. 8,795,741), filed November 21, 2012, which is a continuation of U.S. Serial No. 12/820,866, filed June 22, 2010, and now abandoned, which is a continuation of U.S. Serial No. 12/494,598, filed June 30, 2009, and now abandoned. U.S. Serial No. 13/683,417 is also a continuation of U.S. Serial No. 13/651,660 (now U.S. Patent No. 8,431,163), filed October 15, 2012, which is a continuation of U.S. Application Serial No. 12/821,041 (now U.S. Patent No. 8,293,284), filed June 22, 2010, which is a continuation of U.S. Application Serial No. 12/494,598, filed June 30, 2009, and now abandoned. U.S. Serial No. 14/451,057 is also a division of U.S. Application Serial No. 13/683,444, filed November 21, 2012, which is a division of U.S. Application Serial

No. 12/820,866, filed June 22, 2010, and now abandoned, which is a continuation of U.S. Application Serial No. 12/494,598, filed June 30, 2009, and now abandoned. U.S. Application Serial No. 13/683,444 is also a division of 13/651,660 (now U.S. Patent No. 8,431,163), filed October 15, 2012, which is a continuation of U.S. Application Serial No. 12/821,041 (now U.S. Patent No. 8,293,284), filed June 22, 2010, which is a continuation of U.S. Application Serial No. 12/494,598, filed June 30, 2009, and now abandoned. This application is also a division of U.S. Application Serial No. 13/683,444, filed November 21, 2012, which is a division of U.S. Application Serial No. 12/820,866, filed June 22, 2010, and now abandoned, which is a continuation of U.S. Application Serial No. 12/494,598, filed June 30, 2009, and now abandoned. U.S. Application Serial No. 13/683,444 is also a division of U.S. Application Serial No. 13/651,660 (now U.S. Patent No. 8,431,163), filed October 15, 2012, which is a continuation of U.S. Application Serial No. 12/821,041 (now U.S. Patent No. 8,293,284), filed June 22, 2010, which is a continuation of U.S. Application Serial No. 12/494,598, filed June 30, 2009, and now abandoned. These earlier applications are collectively referred to as the "Parent Applications."

3. I have reviewed an English translation of a document that purports to be a 2008 Belgian marketing authorization for a nitric oxide gas product with the trade name "VasoKINOX"[1], which I am told was made of record in the present application by citation in an Information Disclosure Statement filed on August 25, 2014. I am told that the VasoKINOX document was cited by the U.S. Patent and Trademark Office in an Office action dated April 24, 2013 in a related application, U.S. Application Serial No. 13/683,236. The VasoKINOX document bears the date of July 14, 2008.

4. I made the inventions disclosed and claimed in the present application and in the Parent Applications in the United States prior to July 14, 2008.

[1] Autorisation De Mise Sur Le Marche for VasoKINOX 450 ppm mole/mole issued by the Belgian Federal Agency for Drug and Medical Products (BE 320336), dated 14/07/2008.

5. As an employee of INOT/Ikaria, I served as the Medical Monitor responsible for the design and execution of a multinational, randomized, controlled clinical trial entitled "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," designated as the "INOT22" study. INOT22 was designed and purposed by INOT to compare the diagnostic utility of short-term (10 minute) inhalation of inhaled nitric oxide (iNO) alone, iNO plus oxygen ("O_2"), or O_2 alone to children between the ages of four weeks and eighteen years with either idiopathic pulmonary arterial hypertension, congenital heart disease with pulmonary arterial hypertension, or childhood forms of cardiomyopathy undergoing diagnostic right heart catheterization and acute pulmonary vasodilatation testing, to assess pulmonary vasoreactivity.

6. As evidence of my date of invention, I have attached photocopies of an early INOT22 study protocol "Amendment I" (Appendix 1); an electronic exchange between me and members of the INOT22 study steering committee (Appendix 2); a further amended "Amendment II" INOT22 study protocol (Appendix 3); a letter from INOT to the U.S. Food and Drug Administration ("FDA") (Appendix 4); an electronic exchange between me and Debra A. Rimar with a draft Clinical Study Report[2] attached (Appendix 5); and the prescribing information for INOmax® (nitric oxide) for inhalation published in 2007 (Appendix 6). Certain material irrelevant to the question of date of invention has been redacted from Appendices 2, 4, and 5. In the remaining material of Appendices 2, 4, and 5, and in Appendices 1 and 3, all dates have been redacted; all of these redacted dates are prior to July 14, 2008.

7. Appendix 1 is a copy of an early INOT22 study protocol ("Amendment I") that did not exclude from the study patients with pre-existing left ventricular dysfunction. Exclusion criteria for the study are described at page 21 of Appendix 1. *See*, § 9.3.2. At that point in the INOT22 study, patients were excluded from enrollment if any of the following were true:

[2] The highlighted text that appears in a few places in the draft Clinical Study Report is original to the draft that was attached to the email exchange.

1. Focal pulmonary infiltrates on chest radiograph.
2. Diagnosed with severe obstructive or restrictive pulmonary disease that is significantly contributing to the patient's pulmonary hypertension.
3. Received treatment with nitric oxide for inhalation within 30 days prior to study initiation, are on other investigational medications, nitroglycerin, sodium nitroprusside, sildenafil, other PDE-5 inhibitors, or prostacyclin.
4. Pregnant (urine HCG +).

8. Appendix 2 is a copy of an email exchange summarizing a teleconference between me and members of the INOT22 study steering committee. During the teleconference, we discussed several serious adverse events (SAEs) that occurred during the early phase of the original INOT22 study, during the time the above four exclusion criteria were being applied. Though not specified in the email, the SAEs associated with item 2 in the email (relating to elevated baseline pulmonary capillary wedge pressure ("PCWP")) included pulmonary edema. During the teleconference, the steering committee agreed to amend the INOT22 study protocol to exclude children with a baseline PCWP of greater than or equal to 20 mmHg, because the committee recognized that iNO may raise the wedge pressure in patients with diastolic dysfunction, and the clinical sequelae are most likely to occur and be most severe in those with an elevated baseline PCWP.

9. Appendix 3 is a copy of a subsequently amended INOT22 study protocol (Amendment II) that, unlike the earlier Amendment I protocol, excludes from the study any patients with baseline PCWP greater than 20 mmHg. Exclusion criteria for the study are described at page 20 of Appendix 3. *See*, § 9.3.2. Patients were excluded from enrollment if any of the following were true:

1. Focal pulmonary infiltrates on chest radiograph.
2. Diagnosed with severe obstructive or restrictive pulmonary disease that is significantly contributing to the patient's pulmonary hypertension.

3. Received treatment with nitric oxide for inhalation within 30 days prior to study initiation, are on other investigational medications, nitroglycerin, sodium nitroprusside, sildenafil, other PDE-5 inhibitors, or prostacyclin.
4. Pregnant (urine HCG +).
5. Baseline PCWP > 20 mmHg.

10. Each of Appendices 1 and 3 states on its respective page 1 (the "Synopsis" page) that the name of the finished product utilized in the INOT22 study was INOmax® (nitric oxide) for inhalation. This is a pharmaceutical product manufactured by INOT as a compressed mixture of nitric oxide and nitrogen gases supplied in an aluminum cylinder. See the section headed "9.4.2 Identity of Investigational Product" at page 22 of Appendix 1 and at page 21 of Appendix 3.

11. Each of Appendices 1 and 3 states in the section headed "9.1 Overall Study Plan and Design" that "**Treatment can also be discontinued at the discretion of the attending physician or following the presentation of an adverse response to study drug.**" See page 19 of Appendix 1 and page 18 of Appendix 3. Each of Appendices 1 and 3 states in the section headed "9.3.3 Removal of Patients from Therapy or Assessment" that "**Treatment may also be discontinued if…the investigator deems it in the best medical interest of the patient.**" See page 21 of Appendix 1 and page 20 of Appendix 3.

12. Appendix 4 is a copy of a letter from INOT informing FDA that the protocol for the INOT22 study was being amended to exclude subjects with a baseline PCWP of greater than 20 mmHg.

13. Appendix 5 is a copy of an email exchange communicating a draft Clinical Study Report for the INOT22 study that I helped author. The Clinical Study Report draft document that was attached to that email exchange is included in Appendix 5. Upon review of the data from the INOT22 study, including (a) the record of SAEs experienced in the period from the

start of the study up to the amendment of the protocol to exclude patients with baseline PCWP greater than 20 mmHg and (b) the record of SAEs experienced in the period from the time the protocol was so amended until the end of the study, I recognized, prior to July 14, 2008, that the risk of pulmonary edema and other SAEs in pediatric patients inhaling nitric oxide gas was higher in patients with pre-existing left ventricular dysfunction (*e.g.*, patients with a baseline PCWP of greater than 20 mmHg) than in those without pre-existing left ventricular dysfunction. This recognition is evidenced by the statement in Appendix 5 at page 77, penultimate paragraph, "**Caution is warranted when using NO with oxygen in patients susceptible to pulmonary edema, i.e., patients with significantly elevated PCWP or other signs of poor LV [left ventricle] function.**" As indicated by the generality of this statement in the draft Clinical Study Report, I realized at the time the draft was prepared that the increased risk of pulmonary edema is not limited to the categories of pediatric patients who were the subject of the INOT22 study and who have pre-existing elevated PCWP or other signs of poor left ventricle function, but rather applies more generally—*e.g.*, encompassing all pediatric patients who are being treated with iNO and oxygen and happen to have pre-existing elevated PCWP or other signs of poor left ventricle function. This certainly includes those patients who are treated in accordance with the sole approved indication for iNO in the U.S.: *i.e.*, neonates with hypoxic respiratory failure who are not dependent on right-to-left shunting of blood, and who are treated with 20 ppm iNO. (Diagnosing hypoxic respiratory failure can be done using standard diagnostic procedures, including echocardiography.) INOT has manufactured and marketed cylinders of compressed nitric oxide in nitrogen for treatment of patients with this indication since before I joined INOT, so use of nitric oxide gas for this indication and at that dosage (more specifically, maintaining the administration of 20 ppm iNO for up to 14 days or until the patient's hypoxia has resolved) was well known to me during my tenure at INOT/Ikaria, including when the Clinical Study Report was drafted. See Appendix 6, a 2007 version of the prescribing information for INOmax®, particularly the "Dosage" section. I realized the newly identified risk means that patients who are candidates for iNO but who are found to have pre-existing left ventricular dysfunction either should be excluded from treatment with iNO and provided a different

treatment, or, if they are given the iNO despite their left ventricular dysfunction, should be monitored for increased PCWP or development of pulmonary edema, and the iNO discontinued if the risk to the particular patient warrants discontinuing. I also was aware prior to July 14, 2008, that alternative therapies for hypoxic respiratory failure exist. These alternative therapies include vasodilators, intravenous fluids, bicarbonate therapy, and mechanical ventilation. See the "Administration" section of the 2007 prescribing information in Appendix 6.

14. The evidence provided in this Declaration shows that the presently claimed method was conceived and reduced to practice prior to July 14, 2008.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date: 10/12/2014

James S. Baldassarre, M.D.

23074906.doc

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

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 $\geq$ 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 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.

3. TABLE OF CONTENTS

4. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Below is a list of abbreviations that are used in this clinical report.

AE	Adverse events
ABG	Arterial Blood Gas
APVT	Acute pulmonary vasodilator testing
BSA	Body Surface Area
CFR	Code of Federal Regulations
CHD	Congenital heart disease
CHF	Congestive heart failure
CI	Cardiac index
CO	Cardiac output
CVPm	Mean central venous pressure
DAP	Diastolic arterial blood pressure
FDA 1572	Statement of Investigator
FDA	Food and Drug Administration
FiO_2	Fraction of inspired oxygen concentration
Hgb	Hemoglobin
HR	Heart rate
HTN	Hypertension
IND	Investigational new drug (application)

INO	Nitric Oxide for Inhalation
IPAH	Idiopathic Pulmonary Arterial Hypertension
IRB	Institutional Review Board
MAP	Mean arterial pressure
MetHgb	Methemoglobin
mmHg	Millimeters of mercury
n	Total number of patients (sample size)
N_2	Nitrogen
NO	Nitric oxide
NO_2	Nitrogen dioxide
O_2	Oxygen
PAP	Pulmonary artery pressure
PAPd	Diastolic pulmonary artery pressure
PAPm	Mean pulmonary artery pressure
PAPs	Systolic pulmonary artery pressure
PAWPm	Mean pulmonary artery wedge pressure
PA Sat	Pulmonary artery oxygen saturation
PCWP	Pulmonary capillary wedge pressure
PH	Pulmonary hypertension
PPH	Primary pulmonary hypertension

ppm	Parts per million, by volume (40 ppm = 0.004% of the inhaled gas)
PVR	Pulmonary vascular resistance
PVRI	Pulmonary vascular resistance index
PV Sat	Pulmonary vein oxygen saturation
SaO_2	Arterial oxygen percent saturation
SAP	Systolic arterial blood pressure
SAPm	Mean Systolic arterial blood pressure
SOP	Standard operating procedure
SpO_2	Oxygen saturation by pulse oximeter
SvO_2	Mixed venous oxygen saturation

Definition of Terms
Below is a list of terms, and their respective definition, used in this report

Body Surface Area (BSA)	Uses the patient's height and weight to calculate the surface area. M^2= SqRt[(cm*kg)/3600]
Cardiac Index (CI)	Normal range: 2.5 to 4 L/min/m^2 The CI assess overall cardiac performance (eliminates body size as a variable). CI = CO/BSA
Cardiac Output (CO)	Normal range: 4 to 8 L/min The cardiac output is the product of stroke volume and heart rate and can be measured by: thermo dilution if no shunts or the Fick equation (using measured VO_2 for patients with our without shunts).

Fick Equation:

By measuring the amount of oxygen consumed by the tissues and the arterial-venous oxygen content difference, the cardiac output can be determined.
Fick equation:

$CO = VO_2/min / CaO_2 - CvO_2$

VO_2/min = total tissue extraction of oxygen per minute

CaO_2 = arterial content of oxygen (mL/L)

CvO_2 = venous content oxygen (mL/L)
(CaO_2 may be SaO_2 and CvO_2 may be SvO_2)

Pulmonary Vascular Resistance (PVR):

PVR (dynes/sec/cm^5) =
(PAPm – PAWP)/CO

Normal range: 〈 2 units. The PVR is a useful parameter in assessing right ventricular afterload.

(dynes/sec/cm^3 = Woods unit
(Hg/L/min)/80)

Pulmonary Vascular Resistance Index (PVRI):

Normal range: 〈 3u•m^2
The PVRI utilizes the cardiac (CI) instead of the cardiac output (CO)

PVRI = (PAPm – PAWP)/CI

Pulmonary Hypertension:

A condition characterized by elevated pulmonary artery pressure, associated with changes in the pulmonary vascular bed. PAPm is greater than 25 mmHg at rest or 30 mmHg during exercise.

Reversible Pulmonary Hypertension

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%)

5. ETHICS

5.1 Institutional Review Board (IRB) / Independent Ethics Committee (IEC)

The protocols and local Informed Consent Forms must be reviewed and approved by each of the participating institutions' Institutional Review Board (IRB) / Independent Ethics Committee (IEC) prior to the initiation of patient accrual. The IRB/IEC must be notified of all subsequent protocol amendments. In addition, progress reports will be submitted to the IRB/IEC by the investigator as indicated by IRB/IEC's guidelines. Each Institutional Review Board / Independent Ethics Committee must meet the United States Food and Drug Administration's (FDA's) and/or ICH requirements for composition, documentation, and operational procedures.

The Investigator shall provide the Sponsor with the IRB/IEC's written notification of approval along with the IRB/IEC membership list and/or statement that the IRB/IEC operates in accordance with GCPs.

5.2 Ethical Conduct of the Study

The study will be conducted in accordance with the principles that have their origins in the Declaration of Helsinki, as well as International Conference on Harmonization Good Clinical Practices Guidelines (ICH GCP) and applicable regulatory requirements.

5.3 Patient Information and Informed Consent

The informed consent must contain all elements required by the FDA under 21 CFR part 50 and/or ICH Guidance for Good Clinical Practice – E6 section 4.8 as well as any other elements required by local and institutional policies. All patients, (or legally authorized representative) must provide written consent after having had adequate time to consider their participation in the study. Consent must be obtained prior to any protocol related procedures that are not part of the patient's normal care. Written documentation of consent must be provided via the signature page. The patient or their legal representative must receive a signed copy of the consent form according to ICH GCP guidelines. The exact definition of legal representative should be determined for a hospital by its

Institutional Review Board / Independent Ethics Committee in compliance with local and state statutes.

5.4 Financial Interest Statement

In anticipation of utilizing this study for US regulatory submission, each investigator will complete and submit a Financial Interest Disclosure statement detailing all financial involvement with the Sponsor (including other research grants, stock, consultation fees, etc.) as required by FDA 21 CFR 54.4.

6. INVESTIGATORS AND STUDY ADMINISTRATION STRUCTURE

6.1 Investigators

Approximately 8 sites will participate in the trial with an expected total enrollment of a minimum of 150 patients (approximately 20 patients per site). Enrollment will proceed until at least 25 patients per entry diagnosis are enrolled.

6.2 Administrative Structure

This study was established by the INO Therapeutics (the sponsor). A steering committee will review the contents of the protocol and subsequent amendments, monitor the progress of the trial, and provide recommendations to the sponsor on changes in the procedures and conduct of the trial.

6.3 Steering Committee Members

David Wessel, MD	Boston Children's Hospital, Massachusetts, USA
Robyn Barst, MD	Columbia Presbyterian Hospital, New York, USA
Duncan Macrae, MD	Royal Brompton Hospital, London, England

6.4 Data Safety and Monitoring Board Members

The NIH and many other institutions require that the study protocol specify a plan for the data and safety monitoring of the trial. Typically, the level of oversight is determined by the risks, complexity and duration of the proposed investigation, and the plan must be approved by the appropriate IRBs.

DSMBs have not been commonly established for short-term studies of interventions to relieve symptoms or to confirm diagnoses. Because the primary endpoints of such studies are not serious irreversible events, as in a major outcome study, the ethical issues for

monitoring are different. Early termination for effectiveness is rarely appropriate in such studies.

Given the nature of the proposed investigation, the very short duration of exposure, the endpoints being studied, the number of patients and the duration of treatment, no interim analysis for efficacy will be conducted. Although the adverse event profile of inhaled NO has been well characterized in newborn infants, and to a lesser extent in the target population for this investigation, all possible risks cannot be predicted with certainty. To ensure the well being of patients enrolled in the trial, safety of all patients will be monitored on an ongoing basis. All adverse events and serious adverse events will be reviewed with the steering committee on a regular basis, and will be reported to the appropriate health authorities, and IRBs/IEC as per ICH GCP and as required by local regulations.

7. INTRODUCTION

Pulmonary hypertension (PH) is a condition characterized by elevated pulmonary artery pressures. Pulmonary hypertension may be idiopathic (i.e., without an identified cause), or secondary to other disease processes (e.g. intrinsic heart or lung disease, collagen-vascular disease, toxins or infections). In either case, it is associated with changes in the pulmonary vascular bed such as vasoconstriction, vascular-wall remodeling and thrombosis *in situ* resulting in increased vascular resistance. Abnormal production of vasorelaxants and vasoconstrictors by the pulmonary endothelium may also play a role. Endothelium-derived metabolite imbalances of the vasorelaxant prostacyclin and vasoconstrictor thromboxane have been linked to PH, as have impaired synthesis of vasorelaxant nitric oxide and enhanced production of vasoconstrictor endothelin. [1, 2, 3] Conventional medical treatments consisting of vasodilators, inotropes, anticoagulants, diuretics or oxygen, are aimed at decreasing mean pulmonary artery pressure (PAPm) and pulmonary vascular resistance (PVR). In patients with primary pulmonary hypertension and symptomatic right ventricular failure, the median survival time is less than 3 years. Surgical intervention such as heart or heart/lung transplantation may have to be considered.[9]

For patients with right ventricular failure and lung disorders, the prognosis and course of treatment are determined by acute pulmonary vasodilation testing (APVT). A reduction in the mean pulmonary artery pressure (PAPm) and pulmonary vascular resistance (PVR) with acute vasodilator treatment may be used to predict therapeutic efficacy of long-term vasodilator medication. Acute pulmonary vasodilation testing is also used to evaluate patients being considered for heart or heart/lung transplantation; elevated pulmonary artery pressures and pulmonary vascular resistance place a strain on the right ventricle leading to an increased risk of perioperative morbidity and mortality due to right heart failure post heart transplant. [4, 5, 6]

Administration of 100% supplemental O_2 has been a standard in acute pulmonary vasodilation testing, especially in pediatrics. However, some patients with reactive pulmonary vasculature fail to respond to acute treatment with 100% supplemental O_2. It has been shown that combination testing with inhaled nitric oxide and oxygen provides additional pulmonary vasodilation in patients with a reactive vascular bed.[7]

Nitric oxide (INOmax®) is FDA approved for use in term newborns with pulmonary hypertension and hypoxic respiratory failure in conjunction with mechanical ventilation and other supportive measures to allow more blood to circulate in the lung, which helps increase blood oxygen levels. (Investigators Brochure, INO Therapeutics) Nitric oxide (NO), the endothelial-derived relaxing factor is a major physiologic regulator of endothelial smooth muscle tone. In published studies, nitric oxide for inhalation has been shown to reduce pulmonary artery pressures in patients with the adult respiratory distress syndrome, chronic obstructive lung disease, pulmonary hypertension, and congenital heart disease.[4,5,7,8]. In primary and secondary forms of pulmonary hypertension, studies have shown that short-term nitric oxide for inhalation can selectively reduce both PAPm and PVR with minimal side effects.[4,7] Nitric oxide for inhalation has a short half-life, as it quickly binds to hemoglobin within the pulmonary capillary lumen to form methemoglobin, rendering it inactive, and the systemic vasodilation effects are minimal. Potential risks of nitric oxide are rebound pulmonary hypertension, increased nitrogen dioxide levels (a lung irritant), and methemoglobinemia. However, due to the short duration of delivery in this study, it is unlikely these events will occur.

This study will test the hypothesis that a combination of inhaled nitric oxide and oxygen is more sensitive than 100% supplemental oxygen alone in detecting pulmonary vasoreactivity in patients with pulmonary hypertension.

8. STUDY OBJECTIVES

The primary objective of the trial is to compare the number of patients with reversible pulmonary hypertension (vasoreactivity) due to nitric oxide for inhalation and oxygen as compared to 100% oxygen. The criteria for response are:

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%)

The additional objectives of the trial are to compare the incidence and types of drug related and serious adverse events as well as the number of patients with reversible pulmonary hypertension due to nitric oxide for inhalation alone compared to 100% oxygen and to oxygen with nitric oxide for inhalation.

9. INVESTIGATIONAL PLAN

9.1 Overall Study Plan and Design

This trial will be an open, prospective, multi-center, randomized, controlled trial that will compare the utility and side effects of oxygen, nitric oxide and a combination of nitric oxide and O_2 in determining pulmonary reactivity. Each patient will be screened for enrollment and fulfill all entry criteria described in section 9.3. Upon obtaining informed consent approved by the institution's IRB/IEC, patients will be randomly assigned, using a randomization table, to receive either nitric oxide for inhalation at 80 ppm or 100% O_2 as their initial dose. The patients will either be under general anesthesia or awake sedation (mild sedation). Once the study drug delivery equipment is prepared, baseline data will be collected. Using a calibrated INOvent®, either nitric oxide for inhalation at 80 ppm or 100% O_2 will be continuously administered to the patient for ten minutes followed by data collection. The second dose will be the same as the first dose with the addition of either 80 ppm nitric oxide for patients receiving O_2, or 100% O_2 for patients receiving nitric oxide. This dose of 80 ppm NO and 100% O_2 will be delivered for ten minutes followed by data collection. There will be a ten-minute wash out period following this administration. Baseline data will again be collected followed by a ten minute administration of either 80 ppm nitric oxide or 100% O_2. The study drug delivered for this third administration will be the one that was not randomly assigned for the initial study drug administration.

For each patient, NO_2 levels will be monitored throughout the treatment period. Treatment with study gas will be discontinued if NO_2 levels exceed 3 ppm. Treatment can also be discontinued at the discretion of the attending physician or following the presentation of an adverse response to study drug. All adverse reactions will be recorded while on study gas. Serious adverse events will continue to be recorded during the treatment period through day 1 or discharge from the hospital, whichever comes first. Qualification and reporting of all serious adverse events will occur as per the Code of Federal Regulations (CFR) and ICH guidelines.

One appointed clinical staff member at each site will be responsible for the set up and use of the treatment gas delivery system. This individual may also be responsible for maintaining drug accountability records for the sponsor.
Following the acute diagnostic procedure, a brief follow up contact will be made on each patient to determine the vital status 1 year after the diagnostic procedure.

9.2 Discussion of Study Design

This is an open, randomized, prospective, multi-center, controlled trial to demonstrate which diagnostic treatment is most capable of identifying patients with a reactive pulmonary vascular bed. Each patient will serve as his/her own control, receiving all three treatment regimens: 80 ppm nitric oxide for inhalation, 80 ppm nitric oxide and 100% O_2, and the comparison treatment, 100% O_2. Due to the short half-life of NO, a 10 minute washout period following the nitric oxide for inhalation and 100% O_2 treatment will allow sufficient time for elimination of the drug effect before the administration of the comparison treatment.

9.3 Selection of Study Population

The expected population to be enrolled in this study will include patients with Idiopathic Pulmonary Arterial Hypertension, CHD (with or without intravascular shunt) with pulmonary hypertension, and cardiomyopathies. Patients will be stratified based on entry diagnosis. Patients who are either under general anesthesia or awake sedation will be included.

9.3.1 Inclusion Criteria

The patient must meet the following criteria:

1. Have any one of the three disease categories:
    a. Idiopathic Pulmonary Arterial Hypertension
        i. PAPm › 25mmHg at rest, PCWP ≤ 15mmHg, and PVRI › 3 u· m^2 or diagnosed clinically with no previous catheterization.
    b. CHD with pulmonary hypertension repaired and unrepaired,
        i. PAPm › 25mmHg at rest, and PVRI › 3 u· m^2 or diagnosed clinically with no previous catheterization

c. Cardiomyopathy

i. PAPm › 25mmHg at rest, and PVRI › 3 u•m^2 or diagnosed clinically with no previous catheterization.

2. Scheduled to undergo right heart catheterization to assess pulmonary vasoreactivity by acute pulmonary vasodilation testing.
3. Males or females, ages 4 weeks to 18 years, inclusive
4. Signed IRB/IEC approved informed consent (and assent if applicable).

9.3.2 Exclusion Criteria

The patient will be excluded from enrollment if any of the following are true:

1. Focal pulmonary infiltrates on chest radiograph.
2. Diagnosed with severe obstructive or restrictive pulmonary disease that is significantly contributing to the patient's pulmonary hypertension.
3. Received treatment with nitric oxide for inhalation within 30 days prior to study initiation, are on other investigational medications, nitroglycerin, sodium nitroprusside, sildenafil, other PDE-5 inhibitors, or prostacyclin.
4. Pregnant (urine HCG +).

9.3.3 Removal of Patients from Therapy or Assessment

Study gas will be discontinued if NO_2 levels exceed 3 ppm. Alarms on the INOvent® exist to alert clinical personnel when NO_2 levels > 3 ppm. Treatment may also be discontinued if the patient (or legal representative) withdraws their consent or the investigator deems it in the best medical interest of the patient.

9.4 Treatments

9.4.1 Treatments Administered

After obtaining a signed informed consent form, each patient will receive either nitric oxide for inhalation administered using an INOvent® delivery system, or 100% O_2. The INOvent® is designed to add nitric oxide at preset levels to a ventilator circuit so that inspired NO concentrations remain unchanged despite changes in ventilation modes.

- Patients who are under general anesthesia will be intubated and receive nitric oxide for inhalation, 100% O_2 or a combination of NO and O_2. The NO will be administered using an INOvent® delivery system through a t-connector downstream of the inspiratory limb of a mechanical ventilator.

- Patients who are under awake sedation (mild sedation) will receive nitric oxide for inhalation, 100% O_2 or a combination of NO and O_2. The NO will be administered using an INOvent® delivery system through a properly fitted, sealed facemask.

Each patient will be randomized as to which study drug (80 ppm NO or 100%O_2) they will receive as the initial dose. The second dose administration will be 80ppm NO for inhalation with 100% O_2 (set - approximate oxygen delivery 90%) and the third dose administration will be whichever study drug was not initially administered (NO or 100% O_2). There will be a ten-minute wash out period between the second and third dose administration.

9.4.2 Identity of Investigational Product

The active drug, nitric oxide for inhalation, will be manufactured by INO Therapeutics. Nitric oxide for inhalation will be supplied in size "88" aluminum cylinders or equivalent at a concentration of 800 ppm, balance nitrogen (99.92% grade 5 nitrogen, 0.08% pharmaceutical grade nitric oxide). The cylinders should be stored in a controlled, limited access area at standard room temperature. Cylinders labels will distinguish among sites but will not be pre-assigned patient numbers. The oxygen used in this study will be provided by each hospital.

9.4.3 Method of Assigning Patients to Treatment Groups

Randomization of the initial study administered will be a block randomization by site. Only the first treatment assignment will be randomized. The randomization codes will be provided to sites in individual envelopes per patient. Patients will be serving as their own control and will receive all three treatments.

9.4.4 Selection of Doses in the Study

While varying doses of NO for inhalation have been shown to be safe and effective in decreasing PAPm and PVRI, the use of 80 ppm may elicit a response in a small percentage of the non-responders to lower doses. (Wessel D, personal communication, [redacted]) Therefore, 80 ppm of NO for inhalation will be used in an effort to capture data from the maximum number of potential responders. Previous short duration studies with 80 ppm nitric oxide for inhalation have shown no significant increase in the levels of methemoglobin.[7,8]

9.4.5 Selection and Timing of Dose for Each Patient

Once informed consent is obtained, the delivery equipment will be set up with the appropriate study drug cylinders. Doses of 80 ppm NO for inhalation, 100% supplemental O_2 and 80 ppm NO for inhalation with 100% O_2 (set - approximate oxygen delivery 90%) will be administered for at least 10 minutes. The order of the initial treatment will be randomized. The second dose administered will always be 80 ppm NO for inhalation with 100% O_2 followed by a ten minute wash out period. The third dose will be the treatment that was not randomly assigned for the initial study drug administration.

9.4.6 Treatment Group Assignment Blinding

Treatment will not be blinded. Prior to initial baseline measurements, the cardiac catheter will be placed and the drug delivery equipment prepared. The lack of a placebo and the nature of the data being collected (e.g. hemodynamic variables) are expected to be sufficiently objective to eliminate investigator bias.

9.4.7 Prior and Concomitant Therapy

Patients who have received treatment with nitric oxide for inhalation within 30 days prior to study initiation, other investigational medications, nitroglycerin, sodium nitroprusside, sildenafil or other PDE-5 inhibitors or prostacyclin are excluded from this trial.

Ketamine should not be used as part of the anaesthetic regimen.

Concomitant medications are to be recorded on the case report form.

9.4.8 Treatment Compliance

It is the principal investigator's responsibility to ensure that the treatment, as detailed in the approved protocol, is administered to each enrolled patient. The investigator must administer the drug only to patients under the investigator's (or responsible sub-investigator) direct supervision. All drug used in the study must be accounted for and documented in a usage log provided by the sponsor.

9.5 Efficacy and Safety Variables

9.5.1 Efficacy and Safety Schedule of Assessments

The measurements to be obtained and recorded to measure efficacy and safety are shown in Table 1. The schedule of treatments to be administered is shown in Table 2.

Table 1. Schedule of Assessments

Assessment	Screen	Baseline (Room Air or BL 02)	Study Drug Start	Treatment 1 80 ppm NO or 100% O_2	Treatment 2 80 ppm NO and 100% O_2	Wash Out Period	Baseline-2	Treatment 3 80 ppm NO or 100% O_2
Informed Consent	X							
Demography		X						
Hemoglobin		X						
Hemodynamic[1] Measurements		X		X	X		X	X
Adverse Events[2]				<X>				
Serious Adverse Events[3]				<X>				
Oxygen Consumption		X						
Arterial pH		X						

[1] Hemodynamic measurements: HR, SAP, DAP, MAP, CVPm, PAPs, PAPd, PAPm, PAWPm and CO
[2] Adverse events are to be collected until patient is discontinued from study gas.
[3] Serious adverse events are to be collected through 12 hours after discontinuation of study gas, or discharge, whichever comes first.
Follow up assessment at 1 yr. will consist of telephone call to assess medical therapies or surgical procedures pertaining to pulmonary/cardiac disease, and vital status /date of death if applicable.

Table 2. Schedule of Treatments

	Treatment	Hemodynamic Measurements	Cardiac Output	End of Study Treatment
Baseline 1-Data Collection	Baseline O_2 or Room Air*	X	X	
10 Minute Dose	**80ppm NO or 100% O_2			
Data Collection		X	X	X
10 Minute Dose	NO + 100% O_2			
Data Collection		X	X	X
10 Minute Washout				
Baseline 2-Data Collection	Baseline O_2 or Room Air	X	X	
10 Minute Dose	*80ppm NO or 100% O_2			
Data Collection		X	X	X

*Baseline assessments should be made with the patient breathing room air, whenever possible.
**Randomized: Patients will be randomized to as to which treatment is received first.

9.5.2 Data Collection

Baseline Measurements

1. Compliance with the inclusion/exclusion criteria will be documented.
2. Demographic information will be recorded.
3. Diagnosis (underlying disease) will be noted.
4. Concomitant medications will be recorded.
5. Hemoglobin (Hgb)-(value may be within one week of baseline)
6. arterial pH
7. Hemodynamic Measurements:
   (1) Heart Rate (HR)
   (2) Systolic blood pressure (SAP)
   (3) Diastolic blood pressure (DAP)
   (4) Mean arterial pressure (MAP)
   (5) Mean central venous pressure (CVPm)
   (6) Systolic pulmonary artery pressure (PAPs)
   (7) Diastolic pulmonary artery pressure (PAPd)
   (8) Mean pulmonary artery pressure (PAPm)

(9) Mean pulmonary artery wedge pressure (PAWPm) (or directly measured LA pressure, when accessible)

(10) Cardiac output (CO). Cardiac output will be obtained by either the Fick (collections include: VO_2, PaO_2, SaO_2, PA Sat, SvO_2 and PV Sat) or Thermal Dilution method. The case report form will capture which method of determining the cardiac output was used.

Measurements Following First Treatment Administration

1. Hemodynamic Measurements (HR, SAP, DAP, MAP, CVPm, PAPs, PAPd, PAPm, PAWPm, and CO)
2. Adverse events are to be collected until patient is discontinued from study gas.
3. Serious adverse events will be collected through study day 1 or discharge, whichever comes first.

Measurements Following Second Treatment Administration

- Hemodynamic Measurements (HR, SAP, DAP, MAP, CVPm, PAPs, PAPd, PAPm, PAWPm, and CO)

Measurements Following Third Treatment Administration

- Hemodynamic Measurements (HR, SAP, DAP, MAP, CVPm, PAPs, PAPd, PAPm, PAWPm, and CO)
- Arterial pH

Measurements 1 year after the diagnostic procedure

- Therapies received since the diagnostic procedure

- Date of surgery (if any)
- Vital status and date of death, if applicable

Procedures for Maintenance of Baseline Oxygen Saturation Levels

Adjustments will need to be made to maintain the patients baseline oxygen saturation level and to avoid the administration of a hypoxic gas mixture. This should be done before and after each treatment.

Awake Sedation Patients

Patients Not on Supplemental O_2

1. Right heart catheterization.
2. Place properly fitted, sealed facemask on patient (check for leaks).
3. Using 21% oxygen, adjust flow to 15 L/min.
4. Allow for a 10-minute equilibrium period.
5. Take baseline hemodynamic measurements.
6. Note patient's SpO_2 reading and analyzed O_2 reading (INOvent monitor).
7. Start treatment (80 ppm NO or 100% O_2 as per randomization table).
8. After 1 minute, adjust oxygen blender to maintain the patient's baseline analyzed O_2 reading. For the nitric oxide for inhalation treatment, expect a 10% decrease in the patient's FiO_2. During this treatment, you may adjust the blender setting by 10% so as to maintain the baseline O_2 reading.
9. Maintain treatment for 10 minutes.
10. Take hemodynamic measurements.
11. Start second treatment by adding either 80 ppm NO or 100% O_2 so that the administered treatment is a combination of 80 ppm NO and 100% O_2.
12. Maintain treatment for 10 minutes.
13. Take hemodynamic measurements.
14. Stop treatment but do not remove facemask until completion of the study.
15. Adjust oxygen blender to maintain monitored FiO_2 reading of 21%.

16. Do not remove facemask (The facemask will remain in place during the entire procedure. Although it may be loosened during the wash out periods to maintain patient comfort).
17. 10 minute wash out period.
18. Take baseline hemodynamic measurements
19. Start third treatment of either 80 ppm NO or 100% O_2. The third treatment will be whichever study gas was not administered during the first treatment period.
20. Maintain treatment for 10 minutes.
21. Take hemodynamic measurements.
22. Stop treatment.
23. Adjust oxygen blender to maintain monitored FiO_2 reading of 21%.
24. Allow for a ten-minute equilibrium period.
25. Remove facemask from patient.

Patients on Supplemental O_2

1. Obtain patients baseline oxygen saturation levels (pulse oximetry) with patient's supplemental oxygen in place.
2. Right heart catheterization
3. Place properly fitted, sealed face mask on patient (check for leaks)
4. Adjust the patient's O_2 to match delivery they were receiving through nasal cannula prior to study enrollment using the following conversion table as a guide (or titrate FiO_2 to maintain baseline SpO_2):

L/min	0	1	2	3	4	5	6
O_2 (%)	21	25	29	33	37	41	45

5. Re-check patient's O_2 saturation level. It should be the same as initial value, if not, adjust the blender accordingly.
6. Note analyzed O_2 reading from INOvent.
7. Allow for a 10-minute equilibrium period.
8. Take baseline hemodynamic measurements.
9. Start treatment (80 ppm NO or 100% O_2 as per randomization table).
10. After 1 minute adjust the oxygen blender to maintain the baseline SpO_2.
11. Note analyzed O_2 reading from INOvent.
12. Maintain treatment for 10 minutes.

13. Take hemodynamic measurements.
14. Start second treatment by adding either 80 ppm NO or 100% O_2 so that the administered treatment is a combination of 80 ppm NO and 100% O_2.
15. Maintain treatment for 10 minutes.
16. After 1 minute adjust the oxygen blender to maintain the baseline SpO_2.
17. Take hemodynamic measurements
18. Stop treatment but do not remove facemask until completion of study.
19. Adjust oxygen blender to maintain baseline SpO_2
20. Do not remove facemask (The facemask will remain in place during the entire procedure. Although it may be loosened during the wash out periods to maintain patient comfort)
21. 10 minute wash out period
22. Take baseline hemodynamic measurements
23. Start third treatment of either 80 ppm NO or 100% O_2. The third treatment will be whichever study gas was not administered during the first treatment period.
24. After 1 minute adjust oxygen blender to maintain baseline SpO_2.
25. Take hemodynamic measurements.
26. Stop treatment.
27. Adjust oxygen blender to maintain baseline SpO_2.
28. Allow for a ten-minute equilibrium period.
29. Remove facemask.
30. Put patient back on nasal cannula administration of supplemental O_2.

Patients Intubated and Under General Anesthesia

Patients Not on Supplemental O_2

1. Patients will be placed under general anesthesia and intubated according to the standard medical care and procedures of the institution.
2. Right heart catheterization.

3. Using 21% oxygen, adjust flow to 15 L/min.
4. Allow for a 10-minute equilibrium period.
5. Take baseline hemodynamic measurements.
6. Note patient's SpO_2 reading and analyzed O_2 reading (INOvent monitor).
7. Start treatment (80 ppm NO or 100% O_2 as per randomization table).
8. After 1 minute, adjust oxygen blender to maintain the patient's baseline analyzed O_2 reading. For the nitric oxide for inhalation treatment, expect a 10% decrease in the patient's FiO_2. During this treatment, you may adjust the blender setting by 10% so as to maintain the baseline O_2 reading.
9. Maintain treatment for 10 minutes.
10. Take hemodynamic measurements.
11. Start second treatment by adding either 80 ppm NO or 100% O_2 so that the administered treatment is a combination of 80 ppm NO and 100% O_2.
12. After 1 minute, adjust oxygen blender to maintain the patient's baseline analyzed O_2 reading.
13. Maintain treatment for 10 minutes.
14. Take hemodynamic measurements.
15. Stop treatment.
16. Adjust oxygen blender to maintain monitored FiO_2 reading of 21%.
17. 10 minute wash out period.
18. Take baseline hemodynamic measurements
19. Start third treatment of either 80 ppm NO or 100% O_2. The third treatment will be whichever study gas was not administered during the first treatment period.
20. After 1 minute, adjust oxygen blender to maintain the patient's baseline analyzed O_2 reading.
21. Maintain treatment for 10 minutes.
22. Take hemodynamic measurements.
23. Stop treatment.
24. Adjust oxygen blender to maintain monitored FiO_2 reading of 21%.
25. Extubation will occur according to each institution's standard of care.

Patients on Supplemental O_2

1. Before intubation and initiation of general anesthesia, obtain patients baseline oxygen saturation levels (pulse oximetry) with patient's supplemental oxygen in place.
2. Patients will be placed under general anesthesia and intubated according to the standard medical care and procedures of the institution.
3. Right heart catheterization
4. Adjust the patient's O_2 to match delivery they were receiving through nasal cannula prior to study enrollment.
2. Re-check patient's O_2 saturation level. It should be the same as initial value, if not, adjust the blender accordingly.
3. Note analyzed O_2 reading from INOvent.
4. Allow for a 10-minute equilibrium period.
7. Take baseline hemodynamic measurements.
8. Start first treatment (80 ppm or 100% O_2 as per randomization table).
9. After 1 minute adjust oxygen blender to maintain baseline SpO_2.
10. Maintain treatment for 10 minutes.
11. Take hemodynamic measurements.
12. Start second treatment by adding either 80 ppm NO or 100% O_2 so that the administered treatment is a combination of 80 ppm NO and 100% O_2.
13. After 1 minute adjust oxygen blender to maintain baseline SpO_2.
14. Maintain treatment for 10 minutes.
15. Take hemodynamic measurements.
16. Stop treatment.
17. Adjust oxygen blender to maintain patient's baseline SpO_2.
18. Ten minute wash out period
19. Take baseline hemodynamic measurements
20. Start third treatment of either 80 ppm NO or 100% O_2. The third treatment will be whichever study gas was not administered during the first treatment period.
21. Adjust oxygen blender to maintain patient's baseline SpO_2.
22. Maintain treatment for 10 minutes.
23. Take hemodynamic measurement.
24. Stop treatment.
25. Adjust oxygen blender to maintain patient's baseline SpO_2.
26. Allow for a ten-minute equilibrium period.
27. Extubation will occur as per each institutions standard of care.

9.5.3 Ventilator Weaning and Extubation Strategy

Following the third treatment administration, study patients under general anesthesia will be weaned from mechanical ventilator and extubated according to standard medical care and hospital specific protocol. Study patients under 'awake sedation' will have the treatments discontinued and facemask removed according to standard medical care and hospital specific protocol.

9.5.4 Appropriateness of Measurements

Demographic and baseline data will be collected and evaluated in an attempt to demonstrate that the treatment groups are well balanced with respect to age, sex, race, and that there were no substantial differences in either population with regards to the underlying disease. The measured and calculated values in this protocol are used in standard clinical practice to assess pulmonary vasoreactivity. Both the PAPm and the PVRI have been shown to be useful parameters in measuring the body's response to vasoactive drug therapy.

9.5.5 Efficacy Variables

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 $\geq$ 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 ≥ 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

9.5.6 Safety Variables

The following safety variables will be assessed throughout the treatment gas administration period:

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

9.5.7 Drug Concentration Measurements

The INOvent® gas delivery system measures the flow of gas in the ventilator circuit and a mass flow controller adds NO to the ventilator gas flow to create the desired concentration. The device continuously samples gas from the side port adapter and measures oxygen, nitric oxide and nitrogen dioxide with electrochemical monitors.

9.6 Data Quality Assurance

Prior to study initiation there will be meetings to prepare investigators and standardize performance at each study center associated with the trial. Data will be collected by the study site coordinator and verified at the site by the clinical research associate (CRA). This data will be monitored and verified 100% to the medical charts. Data will be double key entered into a validated Oracle Clinical database managed by the Sponsor. Discrepancies will be flagged and the database manager will make the decisions regarding the flags. The trial staff at the hospital will make data corrections as necessary

9.7 Statistical Methods Planned and Determination of the Sample Size

See Appendix 2.

9.7.1 Sample Size Determination

The following assumptions are made:

1. The desired type I (α) error of 0.05 is the threshold for statistical significance (2-tailed)
2. The expected percentage of patients who have a reduction in PVR of $\geq$ 20% using 80 ppm NO and 100% O_2 and will have a reduction in PVR of $\leq$ 20% using 100% O_2 will be 24%.[7]
3. The expected percentage of patients who have a reduction in PVR of $\geq$ 20% using 100% O_2 and will have a reduction in PVR of $\leq$ 20% using 80 ppm NO and 100% O_2 will be 0%.[7]
4. The desired power (1 - ß) for the trial is 80%.

Using the assumptions listed above, the minimum number of patients required per entry diagnosis is 25. Enrollment will proceed until at least 25 patients per entry diagnosis are enrolled and there are at least 150 patients in the trial.

9.7.2 Interim Analysis

No interim analysis is planned for this trial.

9.8 Changes in Conduct of the Study or Planned Analyses

Any change in the conduct of the study or planned analyses instituted after the start of the study will be documented. The time and reason for the change, the procedure used to decide on the change, the person or group responsible for the change and the nature and content of the data available when the change is made will be documented whether or not the change was documented as a formal protocol amendment.

10. ADMINISTRATIVE DETAILS

10.1 Accountability of Study Drug and Equipment

Drug receipt, return and usage logs for the clinical supplies must be maintained by the investigator at the study site to assure accountability of all gas cylinders supplied. This documentation must include the patient number, cylinder serial number, date the treatment gas was received, date the gas was dispensed, amount used, amount remaining in stock, and date treatment gas was returned. The documents will be reviewed at each monitoring visit.

It is prohibited to use drugs or medical devices supplied by INO Therapeutics specifically for use in this protocol for patients not enrolled in this protocol.

10.2 Case Report Forms

All case report forms are to be completed within one month after patient completion of the study. A case report form is provided for each patient. All forms are to be filled out in black ink or typed.
Correction(s) of data on the case report form should be made by crossing out the incorrect data (in a manner that leaves the previous entry identifiable) and writing the correct values next to those crossed out. Each correction must be initialed and dated by the individual making the correction.

10.3 Investigator Requirements

Prior to study initiation, the investigator will complete and submit to INO Therapeutics Inc. all documents required by the FDA 21 CFR Part 50, 56, and 312 and ICH GCP (E6) section 8.0. Additionally, each investigator must assure the following:

- An Institutional Review Board (IRB) / Independent Ethics Committee (IEC) that complies with the requirements set forth in 21 CFR Part 50 and 56 of FDA regulations or ICH GCP (E6) section 3.0 will be responsible for the initial and continuing review and approval of the proposed clinical study.

- Prompt reporting to the IRB / IEC all changes in research activity and all unanticipated problems involving risks to human patients or others, and that he/she will not make any changes in the research until the IRB / IEC has approved the changes and INO Therapeutics, Inc. has notified the FDA and/or appropriate regulatory agency, as required by 21 CFR 56 and 312.30 or ICH GCP (E6) section 4.5 and 4.10. Documentation of approval must be forwarded to INO Therapeutics for any amendment requiring IRB/IEC approval.
- Reporting to IRB/IEC at least yearly on the progress of the investigation and within three months after completion, termination or discontinuation of the study.
- Ongoing evaluation, management and reporting of adverse experiences.
- Submission of a Financial Interest Disclosure statement detailing all financial involvement with the Sponsor (including other research grants, stock, consultation fees, etc.) as required by 21 CFR 54.

10.4 Recording of Adverse Events

Each patient will be assessed for any new or continuing adverse events by the clinical investigator and the study coordinator. An adverse event is defined as any untoward medical occurrence in a patient/subject of a clinical investigation that involves the administration of a pharmaceutical product. The event need not have a causal relationship with the treatment. This includes any events that are not seen at baseline or, if present at baseline, have worsened in severity. Any adverse event reported by the caregiver or noted by the investigator or study coordinator will be recorded on the Adverse Event pages on the case report form. The severity and drug relationship will be determined, and any management required will be recorded. The adverse event will be followed until resolution or discontinuation of the study drug, whichever occurs first. The investigator will review the clinical laboratory test results in a timely fashion. Only those results qualifying as adverse events, as defined above, will be recorded on the Adverse Event section of the case report form.

10.4.1 Study Drug Relationship

The investigator is responsible for assessing the causal relationship between any events and the study treatment. Additionally, the investigator is responsible for providing appropriate treatment for the event and for adequately following the event until resolution. The clinical investigator should determine the study drug relationship using the following explanations:

Not Related

The event is clearly related to other factors such as the patient's/subject's clinical state, therapeutic interventions, or concomitant drugs administered to the patient/subject.

Remote

The event was most likely produced by other factors such as the patient's/subject's clinical state, therapeutic interventions or concomitant drugs administered to the patient/subject, and does not follow a known response pattern to the study drug.

Possible

The event follows a reasonable temporal sequence from the time of drug administration and/or follows a known response pattern to the study drug, but could have been produced by other factors such as the patient's/subject's clinical state, therapeutic interventions or concomitant drugs administered to the patient/subject.

Probable

The event follows a reasonable temporal sequence from the time of drug administration and follows a known response pattern to the study drug and cannot be reasonably explained by other factors such as the patient's/subject's clinical state, therapeutic interventions or concomitant drugs administered to the patient/subject.

Highly Probable

The event follows a reasonable temporal sequence from the time of drug administration and follows a known response pattern to the study drug and cannot be reasonably explained by other factors such as the patient's/subject's clinical state, therapeutic interventions or concomitant drugs administered to the patient/subject and either occurs immediately following study drug administration, or improves on stopping the drug, or reappears on repeat exposure, or there is a positive reaction at the application site.

Temporal sequence is defined as an association between the suspect drug and the observed reaction or event in which the suspect drug was present prior to the reaction or event as defined by history or blood level of drug.

Study drug(s) includes the drug(s) under evaluation, the reference drug(s), placebo, or any other drug(s) required by the protocol.

Severity of an adverse event will be defined from the qualitative assessment of the degree of intensity of the event as determined by the investigator or as reported to him/her by the patient/subject. The assessment of severity is made irrespective of drug relationship or seriousness of the event and should be evaluated according to the following scales:

1 = **Mild** - awareness of the symptom but easily tolerated

2 = **Moderate** - discomfort enough to interfere with normal activities

3 = **Severe** - Incapacitating with the inability to perform normal activities

10.4.2 Serious Adverse Events

A serious adverse event is defined as any event that at any dose: results in death, is life-threatening, results in persistent or significant disability / incapacity, requires or prolongs inpatient hospitalization, or is a congenital anomaly. Important medical events that without medical or surgical intervention would also have resulted in one of the outcomes listed above are also considered a serious adverse event All serious adverse events occurring during the study, and within 12 hours of the discontinuation of treatment gas, or hospital discharge whichever comes first, must be reported to INO Therapeutics within 24 hours by fax/telephone to:

Catherine Evans

INO Therapeutics Regualtory Affairs Associate

Phone: +001 908 238-6655

Fax: +001 908 238-6635

If you have specific questions regarding an adverse event being classified as serious, you may contact the Medical Monitor for this study:

James S. Baldassarre, MD

INO Therapeutics Senior Director of Research & Development

Phone: +001 908 238-6363

Cell: +001 908 500-8111

The patient/subject must be monitored carefully until the condition resolves, reaches a clinically stable endpoint and/or the etiology is identified. The initial telephone contact will be followed within 24 hours by completing an SAE packet with detailed descriptions of the event and supported as needed with written copies of hospital case reports, autopsy reports, and other documents when applicable.

All serious and unexpected adverse events must be reported to the IRB/IEC and appropriate local regulatory agency in writing.

10.4.3 Unexpected Adverse Events

An unexpected adverse event is any event that is not identified in nature, severity or frequency in the current investigator's brochure.

10.5 Records Retention

In compliance with GCPs and both U.S. Federal law and ICH guidelines, copies of all records (e.g., informed consent documents, laboratory data slips, source documents, IND safety reports, test article dispensing records, etc.) which support case report forms of this study, must be retained in the files of the responsible investigator for a minimum of two years following notification by INO Therapeutics that all investigations at all sites are completed, terminated, or discontinued, or that the Food and Drug Administration or other appropriate regulatory agency has approved the New Drug Application. If the investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the

responsibility. INO Therapeutics, Inc. must be notified in writing of the name and address of the new custodian.

10.6 Monitoring and Audits

The study will be periodically monitored/audited by a representative of INO Therapeutics, Inc. It is the responsibility of the principal investigator to provide all study records, including case report forms, source documentation, etc., to the monitor at their visit.

The United States Food and Drug Administration, in the person of a scientifically trained and properly authorized employee of the Agency, or a representative of the local regulatory agency may request access to all study records, including source documents, for inspection and copying.

10.7 Amendments to the Protocol

Neither the investigator nor INO Therapeutics, Inc. will amend or modify the protocol without written notification of the other. All amendments must be approved by INO Therapeutics prior to implementation. All amendments must be submitted to the to the IRB/IEC as required. The IRB/IEC must approve major amendments prior to implementation at the study site.

10.8 Termination of Trial

It is agreed that, for reasonable cause, either the investigator or the sponsor, INO Therapeutics, Inc. may terminate this study, provided written notice is submitted at a reasonable time in advance of intended termination.

11. REFERENCE LIST

1. Christman BW, McPherson CD, Newman JH, King GA, Bernard GR, Groves BM, Loyd JE. An imbalance between the excretion of thromboxane and prostacyclin metabolites in pulmonary hypertension. *N Engl J Med* 1992; 327:70-75.
2. Giaid A, Saleh D. Reduced expression of endothelial nitric oxide synthase in the lungs of patients with pulmonary hypertension. *N Engl J Med* 1995; 333:214-221.
3. Giaid A, Yanagisawa M, Langleben D, et al. Expression of endothelin-1 in the lungs of patients with pulmonary hypertension. *N Engl J Med* 1993; 328:1732-1739.
4. Rossaint R, Falke KJ, Lopez F, et al. Inhaled nitric oxide for the adult respiratory distress syndrome. *N Engl J Med* 1993; 328:399-405.
5. Adatia I, Thompson J, Landzberg M, et al. Inhaled nitric oxide in chronic obstructive lung disease. *Lancet* 1993; 341:307-308.
6. Kinsella JP, Neish SR, et al. Low dose inhalational nitric oxide in persistent pulmonary hypertension of the newborn. *Lancet* 1992; 340:819-820.
7. Atz AM, Adatia I, Lock JE, Wessel DL. Combined effects of nitric oxide and oxygen during acute pulmonary vasodilator testing. *J Am Coll Cardiol* 1999; 33(3): 813-9.
8. Dellinger RP, Zimmerman JL, Taylor RW, Straube RC, et al. Effects of inhaled nitric oxide in patients with acute respiratory distress syndrome: Results of a randomized phase II trial. *Crit Care Med* 1998; 26:15-23
9. Chatterjee K, De Marco T, et al. Pulmonary Hypertension: Hemodynamic Diagnosis and Management. *Arch Intern Med* 2002; 162:1925-1933

APPENDIX 1. PROTOCOL VERSIONS

Protocol Versions:

[redacted]

APPENDIX 2. ANALYTIC PLAN

A. Analysis Populations

All efficacy and safety analyses will be done on all patients randomized (an intent-to-treat basis). If the non-evaluable proportion of patients exceeds 5%, then the efficacy analyses will also be performed on the evaluable patients.

Evaluable patients are patients who meet all entry criteria, receive any treatment gas, and have the data available to calculate the efficacy variables.

Intent-to-treat patients will be all patients randomized regardless of actual receipt of treatment gas, the treatment gas actually received, or the appropriateness of their enrollment.

B. Analyses of Baseline Characteristics

Allowing for the fact that all patients will be randomly assigned to each treatment group, any discrepancies in the distributions of baseline characteristics should be considered as random occurrences. However, the distributions of all baseline characteristics (age, sex, race, etc.) will be compared between the two treatment groups.

C. Primary Efficacy Analysis

The primary efficacy variable for this trial is the number of patients that meet response criteria. A positive response is defined 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%)

These variables will be calculated as follows:

% Change in PAPm from Baseline =

$$((PAPm_{Treatment} - PAPm_{Baseline}) / PAPm_{Baseline}) \times 100$$

% Change in PVRI from Baseline =

$$((PVRI_{Treatment} - PVRI_{Baseline}) / PVRI_{Baseline}) \times 100$$

All patients not meeting the above criteria will be counted as having a negative response.

It is hypothesized that the number of patients receiving a combination of NO and O_2 who have a positive response will be significantly greater than the number of patients receiving O_2 alone. The null hypothesis is therefore formerly expressed as:

***H_o*:** There is no difference in the number patients with a positive response in PAPm or PVRI between the NO and O_2 group versus the O_2 alone group.

The alternative hypothesis is:

***H_a*:** A difference exists in the number patients with a positive response in PAPm or PVRI between the NO and O_2 group versus the O_2 alone group.

The difference in the primary efficacy variable(s) between the two treatment groups will be tested using the McNemar Test for Significance of Changes. This test will be conducted with the type I (α) error of 0.05 for statistical significance (2-tailed).

D. Secondary Efficacy Analysis

All tests will be conducted with the type I (α) error of 0.05 for statistical significance (2-tailed).

Number of Patients Who Meet Response Criteria in the NO Group vs. the O_2 Group

This analysis is identical to that outlined the section C of this analytic plan with the exception of the two treatments that will be compared. It is hypothesized that the number of patients receiving NO alone who have a positive response will be significantly greater than the number of patients receiving O_2 alone. The null hypothesis is therefore formerly expressed as:

H_o: There is no difference in the number patients with a positive response between the NO group versus the O_2 alone group.

The alternative hypothesis is:

H_a: A difference exists in the number patients with a positive response between the NO group versus the O_2 alone group.

The difference between the two treatment groups will be tested using the McNemar Test for Significance of Changes. This test will be conducted with the type I (α) error of 0.05 for statistical significance (2-tailed).

Number of Patients Who Meet Response Criteria in the NO Group vs. the NO + O_2 Group

This analysis is also identical to that outlined the section C of this analytic plan with the exception of the two treatments that will be compared. It is hypothesized that the number of patients receiving NO alone who have a positive response will be significantly greater than the number of patients receiving NO + O_2. The null hypothesis is therefore formerly expressed as:

H_o: There is no difference in the number patients with a positive response between the NO group versus the NO + O_2 group.

The alternative hypothesis is:

H_a: A difference exists in the number patients with a positive response between the NO group versus the NO + O_2 group.

The difference between the two treatment groups will be tested using the McNemar Test for Significance of Changes. This test will be conducted with the type I (α) error of 0.05 for statistical significance (2-tailed).

Differences in PVR, PAPm and Cardiac Output in Room Air vs. Each Treatment Group

It is hypothesized that there is a difference in PVRI and PAPm readings between room air (baseline) and each treatment group. The hypotheses are formerly expressed as:

H_o: There is no difference in PVRI between room air (baseline) and the NO + O_2 group.

The alternative hypothesis is:

H_a: A difference exists in PVRI between room air (baseline) versus the NO + O_2 group.

H_o: There is no difference in PVRI between room air (baseline) and the O_2 group.

The alternative hypothesis is:

H_a: A difference exists in PVRI between room air (baseline) versus the O_2 group.

H_o: There is no difference in PVRI between room air (baseline) and the NO group.

The alternative hypothesis is:

H_a: A difference exists in PVRI between room air (baseline) versus the NO group.

H_o: There is no difference in PAPm between room air (baseline) and the NO + O_2 group.

The alternative hypothesis is:

H_a: A difference exists in PAPm between room air (baseline) versus the NO + O_2 group.

H_o: There is no difference in PAPm between room air (baseline) and the O_2 group.

The alternative hypothesis is:

H_a: A difference exists in PAPm between room air (baseline) versus the O_2 group.

H_o: There is no difference in PAPm between room air (baseline) and the NO group.

The alternative hypothesis is:

H_a: A difference exists in PAPm between room air (baseline) versus the NO group.

H_o: There is no difference in cardiac output between room air (baseline) and the NO + O_2 group.
The alternative hypothesis is:
H_a: A difference exists in cardiac output between room air (baseline) versus the NO + O_2 group.

H_o: There is no difference in cardiac output between room air (baseline) and the O_2 group.
The alternative hypothesis is:
H_a: A difference exists in cardiac output between room air (baseline) versus the O_2 group.

H_o: There is no difference in cardiac output between room air (baseline) and the NO group.
The alternative hypothesis is:
H_a: A difference exists in cardiac output between room air (baseline) versus the NO group.

These hypotheses will be tested using the paired t-test if the normality assumption has not been violated, or the Wilcoxon Signed Ranks test if there is a violation of normality. All tests will be conducted with the type I (α) error of 0.05 for statistical significance (2-tailed).

Change in the Ratio of PA Pressure to Systemic Pressure

It is hypothesized that there is a difference in the ratio of PA pressure to systemic pressure between the NO and O_2 group versus the O_2 alone group. The hypotheses are formerly expressed as:

H_o: There is no difference in the ratio of PAPm to SAPm between the NO and O_2 group versus the O_2 alone group.
The alternative hypothesis is:
H_a: A difference exists in the ratio of PAPm to SAPm between the NO and O_2 group versus the O_2 alone group.

The difference in the ratios for each treatment group will be analyzed using an ANOVA model. The list of independent variables includes, but is not limited to, treatment, subject (nested within treatment sequence) and treatment sequence. Differences in treatment will be assessed with the type I (α) error of 0.05 for statistical significance (2-tailed).

Survival at 1 Year Following the Diagnostic Procedure

It is hypothesized that there is a difference in rates of survival at 1 year of those who met response criteria as outlined in section C of this analytic plan. The hypotheses are formerly expressed as:

H_o: There is no difference in the survival rate of patients with a positive response in PAPm or PVRI between the NO and O_2 group versus the O_2 alone group.
The alternative hypothesis is:
H_a: A difference exists in the survival rate of patients with a positive response in PAPm or PVRI between the NO and O_2 group versus the O_2 alone group.

The difference between the two treatment groups will be tested using the Fisher's Exact Test. This test will be conducted with the type I (α) error of 0.05 for statistical significance (2-tailed). In addition, a Kaplan-Meier plots will be generated for time to death for each treatment group.

E. Safety Analysis

Serious Adverse Events

The analysis will be performed on the number and types of serious adverse events reported in each treatment group. The incidence of all serious adverse events, stratified by MEDRA terms, MEDRA body system, and patients with specific serious adverse events will be tabulated. Additionally, the serious adverse events will be stratified by age, sex and race.

H_o: There is no difference in the number of reported serious adverse events between the NO, NO + O_2 and O_2 alone groups.

H_a: A difference exists in the number of reported serious adverse events between the NO, NO + O_2 and O_2 alone groups.

This comparison will be made using Cochran's Test for Related Observations.

Drug Related Adverse Events

The analysis will be performed on the number and types of drug related adverse events reported in each treatment group. The incidence of all drug related adverse events, stratified by MEDRA terms, MEDRA body system, and patients with specific adverse events will be tabulated. Additionally, the adverse events will be stratified by age, sex and race.

H_o: There is no difference in the number of reported drug related adverse events between the NO, NO + O_2 and O_2 alone groups.

H_a: A difference exists in the number of reported drug related adverse events between the NO, NO + O_2 and O_2 alone groups.

This comparison will be made using Cochran's Test for Related Observations.

F. Additional Analyses

All primary methods of analysis have been previously outlined in this document. However, INO Therapeutics reserves the right to perform any additional analyses deemed necessary according to any of the following reasons:

1. Any steering committee or medical monitor recommendations based on investigator concerns.
2. The presence of maldistributed baseline characteristics.
3. The administration of any medications thought to be affecting the treatment as determined by the steering committee and/or the medical monitor.

Additionally, several exploratory analyses will be conducted to determine the existence of any possible relationships between the response variables and diagnosis, delivery system, demographic criteria, etc. Due to the unknown nature of these analyses, INO Therapeutics, Inc. declines to formalize the testing procedures in this analytic plan.

G. Interim Analyses

No interim analysis for efficacy or safety in this study is planned.

APPENDIX 3. LISTING OF AMENDMENT CHANGES

AMENDMENT 1 CHANGES:

Cover Page, Version

Changed From:

"Original Protocol"

Changed To:

"Amendment 1"

Cover Page, Document Date

Changed From:

[redacted]

Changed To:

[redacted]

Cover Page, Study Contact

Deleted: Paul Bridges, European Regulatory Affairs

Changed From:

"Rebecca Light, Clinical Research Manager"

Changed To:

"Jodee Newman, Project Leader"

Synopsis

Changed From:
"Sponsor-INO Therapeutics, Inc."

Changed To:
"Sponsor-INO Therapeutics, LLC"

Changed From:
"Investigators-TBD"

Changed To:
"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 "

Changed From:
"Study Centers-TBD"

Changed To:
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

Secondary Endpoints-Addition:

4) Change in the ratio of PAPm to SAPm by treatment

6) Survival at 1 year by response

4. List of Abbreviations and Definitions of Terms

Addition:
Mean Systolic Arterial blood pressure

Page 14 Section 9.1

Addition:
"Following the acute diagnostic procedure, a brief follow up contact will be made on each patient to determine the vital status 1 year after the diagnostic procedure."

Section 9.5.1 Table 1 - Footnote

Addition:
Assessment-Baseline :Arterial pH
Follow up assessment at 1 yr. Will consist of telephone call to assess medical therapies or surgical procedures pertaining to pulmonary/cardiac disease, and vital status /date of death if applicable.

9.5.2 Data Collection

Addition:
Of Arterial pH to-

Baseline Measurement and Measurements Following Third Treatment Administration

Measurements 1 year after the diagnostic procedure

- Therapies received since the diagnostic procedure
- Date of surgery (if any)
- Vital status and date of death, if applicable

9.5.5 Efficacy Variables

Secondary Endpoints-Addition:

4) Change in the ratio of PAPm to SAPm by treatment

7) Survival at 1 year by response

10.4.2 Serious Adverse Events

Changed From:

Any serious adverse event must be reported to INO Therapeutics within 24 hours by telephone to:

Catherine Evans, Regulatory Affairs Associate

Phone: (908) 238-6655

Fax: (908) 238-6635

Dr. James S. Baldassarre

Phone: (908) 238-6363 Cell: (908) 500-8111

Changed To:

All serious adverse events occurring during the study, and within 12 hours of the discontinuation of treatment gas, or hospital discharge whichever comes first, must be reported within 24 hours to INO Therapeutics by fax/telephone to:

Catherine Evans

INO Therapeutics Regulatory Affairs Associate

Phone: + 001 908 238-6655

Fax: +001 908 238-6635

If you have any specific questions regarding an adverse event being classified as serious, you may contact the Medical Monitor for this study:

Dr. James S. Baldassarre

Phone: +001 908 238-6363

Cell: +001 908 500-8111

Added to text: *"within 24 hours by completing an SAE packet with"*

Delete page 40, second to last paragraph:

All patient/subject deaths will be reported independent of the temporal relationship to the patient's/subject's study participation and treatment (i.e. test drug, placebo).

Appendix 2. Analytic Plan

Section D-page 42/43 Addition:

Change in the Ratio of PA Pressure to Systemic Pressure

It is hypothesized that there is a difference in the ratio of PA pressure to systemic pressure between the NO and O_2 group versus the O_2 alone group. The hypotheses are formerly expressed as:

H_o: There is no difference in the ratio of PAPm to SAPm between the NO and O_2 group versus the O_2 alone group.
The alternative hypothesis is:
H_a: A difference exists in the ratio of PAPm to SAPm between the NO and O_2 group versus the O_2 alone group.

The difference in the ratios for each treatment group will be analyzed using an ANOVA model. The list of independent variables includes, but is not limited to, treatment, subject (nested within treatment sequence) and treatment sequence. Differences in treatment will be assessed with the type I (α) error of 0.05 for statistical significance (2-tailed).

Survival at 1 Year Following the Diagnostic Procedure

It is hypothesized that there is a difference in rates of survival at 1 year of those who met response criteria as outlined in section C of this analytic plan. The hypotheses are formerly expressed as:

H_o: There is no difference in the survival rate of patients with a positive response in PAPm or PVRI between the NO and O_2 group versus the O_2 alone group.
The alternative hypothesis is:
H_a: A difference exists in the survival rate of patients with a positive response in PAPm or PVRI between the NO and O_2 group versus the O_2 alone group.

The difference between the two treatment groups will be tested using the Fisher's Exact Test. This test will be conducted with the type I (α) error of 0.05 for statistical significance (2-tailed). In addition, a Kaplan-Meier plots will be generated for time to death for each treatment group.

INVESTIGATOR AGREEMENT

Protocol INOT22
Version: Amendment I

I have read the protocol, "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", Protocol INOT22 (version 1), and agree to conduct the study as outlined therein. I will make a reasonable effort to conduct the study in a timely and efficient manner and will ensure that all participating staff members are adequately trained to carry out the tasks for which they have been assigned.

I will submit this protocol and all other pertinent information to my IRB/IEC for approval.

_____ _____
Principal Investigator's Signature Date

_____
Name of investigator (printed)

APPENDIX 2

[redacted]

From: Macrae Duncan [mailto:D.Macrae@rbh.nthames.nhs.uk]
Sent: [redacted]
To: James Baldassarre; david.wessel@cardio1.tch.harvard.edu; rjb3@columbia.edu; Mary.Mullen@CARDIO.CHBOSTON.ORG
Cc: Sara.Skinner@inveresk.com; Jodee A. Newman; Sandra.Cottrell@inotherapy.com; Richard Straube
Subject: RE: follow up from teleconference

Dear All,

Sorry to have been unable to make the conference due to an unexpected clinical event.

I can concur with the conclusions circulated. There is an issue around awakening / recovery from anaesthesia in these very fragile patients. If the wrong decisions are made they will rapidly decompensate.

Duncan

-----Original Message-----
From: james.baldassarre@inotherapy.com [mailto:james.baldassarre@inotherapy.com]
Sent: [redacted]
To: david.wessel@cardio1.tch.harvard.edu; rjb3@columbia.edu; Macrae Duncan; Mary.Mullen@CARDIO.CHBOSTON.ORG
Cc: Sara.Skinner@inveresk.com; jodee.newman@inotherapy.com; Sandra.Cottrell@inotherapy.com; richard.straube@inotherapy.com
Subject: follow up from teleconference

Dear all,

just to summarize and ask for confirmation:

1) The number of SAEs is very surprising. In the collective experience of Columbia and Boston Childrens (nearly 2000 procedures) cardio-respiratory arrest is exceedingly rare. Some of the events may be due to the relative inexperience of the operators, and the use of general anaesthesia. Use of NO *perse* doesn't seem to be the major concern. Any investigators added to the trial should be very well experienced.

2) There is a reconized concern that inhaled NO may raise the wedge in patients with diastolic dysfunction, and the clinical sequelae are likely to be most serious in those with an elevated PCWP at baseline (e.g. >/= 20 mmHg). It may be prudent to exclude from the study any child with an elevated baseline PCWP.

3) Cardiomyopathy need not be excluded, given the restriction on baseline wedge pressure

4) Separately from these issues, we propose that kids on bosanten or CCBs may be enrolled in the study. (No change need to the protocol)

5) When we have agreement on these issues, the protocol will be amended.

6) Final note: Jim Baldassarre to meet with Dr Barst re: longer term follow up of kids in this study.

Dr James S. Baldassarre
Sr Director, Clinical Research
INO Therapeutics LLC
O: 908-238-6363
C: 908-500-8111

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:	
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.

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 Hosptital, 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	

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 $\geq$ 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 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 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

[redacted]

[redacted]

4. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Below is a list of abbreviations that are used in this clinical protocol.

AE	Adverse events
ABG	Arterial Blood Gas
APVT	Acute pulmonary vasodilator testing
BSA	Body Surface Area
CFR	Code of Federal Regulations
CHD	Congenital heart disease
CHF	Congestive heart failure
CI	Cardiac index
CO	Cardiac output
CVPm	Mean central venous pressure
DAP	Diastolic arterial blood pressure
FDA 1572	Statement of Investigator
FDA	Food and Drug Administration
FiO_2	Fraction of inspired oxygen concentration
Hgb	Hemoglobin
HR	Heart rate
HTN	Hypertension
IND	Investigational new drug (application)

INO	Nitric Oxide for Inhalation
IPAH	Idiopathic Pulmonary Arterial Hypertension
IRB	Institutional Review Board
MAP	Mean arterial pressure
MetHgb	Methemoglobin
mmHg	Millimeters of mercury
n	Total number of patients (sample size)
N_2	Nitrogen
NO	Nitric oxide
NO_2	Nitrogen dioxide
O_2	Oxygen
PAP	Pulmonary artery pressure
PAPd	Diastolic pulmonary artery pressure
PAPm	Mean pulmonary artery pressure
PAPs	Systolic pulmonary artery pressure
PAWPm	Mean pulmonary artery wedge pressure
PA Sat	Pulmonary artery oxygen saturation
PCWP	Pulmonary capillary wedge pressure
PH	Pulmonary hypertension
PPH	Primary pulmonary hypertension

ppm	Parts per million, by volume (40 ppm = 0.004% of the inhaled gas)
PVR	Pulmonary vascular resistance
PVRI	Pulmonary vascular resistance index
PV Sat	Pulmonary vein oxygen saturation
SaO_2	Arterial oxygen percent saturation
SAP	Systolic arterial blood pressure
SAPm	Mean Systolic arterial blood pressure
SOP	Standard operating procedure
SpO_2	Oxygen saturation by pulse oximeter
SvO_2	Mixed venous oxygen saturation

Definition of Terms
Below is a list of terms, and their respective definition, used in this report

Body Surface Area (BSA)	Uses the patient's height and weight to calculate the surface area. M^2= SqRt[(cm*kg)/3600]
Cardiac Index (CI)	Normal range: 2.5 to 4 L/min/m^2 The CI assess overall cardiac performance (eliminates body size as a variable). CI = CO/BSA
Cardiac Output (CO)	Normal range: 4 to 8 L/min The cardiac output is the product of stroke volume and heart rate and can be measured by: thermo dilution if no shunts or the Fick equation (using measured VO_2 for patients with our without shunts).

Fick Equation:

By measuring the amount of oxygen consumed by the tissues and the arterial-venous oxygen content difference, the cardiac output can be determined.
Fick equation:
$CO = VO_2/min / CaO_2 - CvO_2$
VO_2/min = total tissue extraction of oxygen per minute
CaO_2 = arterial content of oxygen (mL/L)
CvO_2 = venous content oxygen (mL/L)
(CaO_2 may be SaO_2 and CvO_2 may be SvO_2)

Pulmonary Vascular Resistance (PVR):

PVR (dynes/sec/cm^5) =
(PAPm – PAWP)/CO

Normal range: ⟨ 2 units. The PVR is a useful parameter in assessing right ventricular afterload.
(dynes/sec/cm^3 = Woods unit (Hg/L/min)/80)

Pulmonary Vascular Resistance Index (PVRI):

Normal range: ⟨ 3u•m^2
The PVRI utilizes the cardiac (CI) instead of the cardiac output (CO)

PVRI = (PAPm – PAWP)/CI

Pulmonary Hypertension:

A condition characterized by elevated pulmonary artery pressure, associated with changes in the pulmonary vascular bed. PAPm is greater than 25 mmHg at rest or 30 mmHg during exercise.

[redacted]

Reversible Pulmonary Hypertension

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%)

5. ETHICS

5.1 Institutional Review Board (IRB) / Independent Ethics Committee (IEC)

The protocols and local Informed Consent Forms must be reviewed and approved by each of the participating institutions' Institutional Review Board (IRB) / Independent Ethics Committee (IEC) prior to the initiation of patient accrual. The IRB/IEC must be notified of all subsequent protocol amendments. In addition, progress reports will be submitted to the IRB/IEC by the investigator as indicated by IRB/IEC's guidelines. Each Institutional Review Board / Independent Ethics Committee must meet the United States Food and Drug Administration's (FDA's) and/or ICH requirements for composition, documentation, and operational procedures.

The Investigator shall provide the Sponsor with the IRB/IEC's written notification of approval along with the IRB/IEC membership list and/or statement that the IRB/IEC operates in accordance with GCPs.

5.2 Ethical Conduct of the Study

The study will be conducted in accordance with the principles that have their origins in the Declaration of Helsinki, as well as International Conference on Harmonization Good Clinical Practices Guidelines (ICH GCP) and applicable regulatory requirements.

5.3 Patient Information and Informed Consent

The informed consent must contain all elements required by the FDA under 21 CFR part 50 and/or ICH Guidance for Good Clinical Practice – E6 section 4.8 as well as any other elements required by local and institutional policies. All patients, (or legally authorized representative) must provide written consent after having had adequate time to consider their participation in the study. Consent must be obtained prior to any protocol related procedures that are not part of the patient's normal care. Written documentation of consent must be provided via the signature page. The patient or their legal representative must receive a signed copy of the consent form according to ICH GCP guidelines. The exact definition of legal representative should be determined for a hospital by its

Institutional Review Board / Independent Ethics Committee in compliance with local and state statutes.

5.4 Financial Interest Statement

In anticipation of utilizing this study for US regulatory submission, each investigator will complete and submit a Financial Interest Disclosure statement detailing all financial involvement with the Sponsor (including other research grants, stock, consultation fees, etc.) as required by FDA 21 CFR 54.4.

6. INVESTIGATORS AND STUDY ADMINISTRATION STRUCTURE

6.1 Investigators

Approximately 18 sites will participate in the trial with an expected total enrollment of a minimum of 150 patients (approximately 9 patients per site).

6.2 Administrative Structure

This study was established by the INO Therapeutics (the sponsor). A steering committee will review the contents of the protocol and subsequent amendments, monitor the progress of the trial, and provide recommendations to the sponsor on changes in the procedures and conduct of the trial.

6.3 Steering Committee Members

David Wessel, MD	Boston Children's Hospital, Massachusetts, USA
Robyn Barst, MD	Columbia Presbyterian Hospital, New York, USA
Duncan Macrae, MD	Royal Brompton Hospital, London, England

6.4 Data Safety and Monitoring Board Members

The NIH and many other institutions require that the study protocol specify a plan for the data and safety monitoring of the trial. Typically, the level of oversight is determined by the risks, complexity and duration of the proposed investigation, and the plan must be approved by the appropriate IRBs.

DSMBs have not been commonly established for short-term studies of interventions to relieve symptoms or to confirm diagnoses. Because the primary endpoints of such studies are not serious irreversible events, as in a major outcome study, the ethical issues for

monitoring are different. Early termination for effectiveness is rarely appropriate in such studies.

Given the nature of the proposed investigation, the very short duration of exposure, the endpoints being studied, the number of patients and the duration of treatment, no interim analysis for efficacy will be conducted. Although the adverse event profile of inhaled NO has been well characterized in newborn infants, and to a lesser extent in the target population for this investigation, all possible risks cannot be predicted with certainty. To ensure the well being of patients enrolled in the trial, safety of all patients will be monitored on an ongoing basis. All adverse events and serious adverse events will be reviewed with the steering committee on a regular basis, and will be reported to the appropriate health authorities, and IRBs/IEC as per ICH GCP and as required by local regulations.

7. INTRODUCTION

Pulmonary hypertension (PH) is a condition characterized by elevated pulmonary artery pressures. Pulmonary hypertension may be idiopathic (i.e., without an identified cause), or secondary to other disease processes (e.g. intrinsic heart or lung disease, collagen-vascular disease, toxins or infections). In either case, it is associated with changes in the pulmonary vascular bed such as vasoconstriction, vascular-wall remodeling and thrombosis *in situ* resulting in increased vascular resistance. Abnormal production of vasorelaxants and vasoconstrictors by the pulmonary endothelium may also play a role. Endothelium-derived metabolite imbalances of the vasorelaxant prostacyclin and vasoconstrictor thromboxane have been linked to PH, as have impaired synthesis of vasorelaxant nitric oxide and enhanced production of vasoconstrictor endothelin. [1, 2, 3] Conventional medical treatments consisting of vasodilators, inotropes, anticoagulants, diuretics or oxygen, are aimed at decreasing mean pulmonary artery pressure (PAPm) and pulmonary vascular resistance (PVR). In patients with primary pulmonary hypertension and symptomatic right ventricular failure, the median survival time is less than 3 years. Surgical intervention such as heart or heart/lung transplantation may have to be considered.[9]

For patients with right ventricular failure and lung disorders, the prognosis and course of treatment are determined by acute pulmonary vasodilation testing (APVT). A reduction in the mean pulmonary artery pressure (PAPm) and pulmonary vascular resistance (PVR) with acute vasodilator treatment may be used to predict therapeutic efficacy of long-term vasodilator medication. Acute pulmonary vasodilation testing is also used to evaluate patients being considered for heart or heart/lung transplantation; elevated pulmonary artery pressures and pulmonary vascular resistance place a strain on the right ventricle leading to an increased risk of perioperative morbidity and mortality due to right heart failure post heart transplant. [4, 5, 6]

Administration of 100% supplemental O_2 has been a standard in acute pulmonary vasodilation testing, especially in pediatrics. However, some patients with reactive pulmonary vasculature fail to respond to acute treatment with 100% supplemental O_2. It has been shown that combination testing with inhaled nitric oxide and oxygen provides additional pulmonary vasodilation in patients with a reactive vascular bed.[7]

Nitric oxide (INOmax®) is FDA approved for use in term newborns with pulmonary hypertension and hypoxic respiratory failure in conjunction with mechanical ventilation and other supportive measures to allow more blood to circulate in the lung, which helps increase blood oxygen levels. (Investigators Brochure, INO Therapeutics) Nitric oxide (NO), the endothelial-derived relaxing factor is a major physiologic regulator of endothelial smooth muscle tone. In published studies, nitric oxide for inhalation has been shown to reduce pulmonary artery pressures in patients with the adult respiratory distress syndrome, chronic obstructive lung disease, pulmonary hypertension, and congenital heart disease.[4,5,7,8]. In primary and secondary forms of pulmonary hypertension, studies have shown that short-term nitric oxide for inhalation can selectively reduce both PAPm and PVR with minimal side effects.[4,7] Nitric oxide for inhalation has a short half-life, as it quickly binds to hemoglobin within the pulmonary capillary lumen to form methemoglobin, rendering it inactive, and the systemic vasodilation effects are minimal. Potential risks of nitric oxide are rebound pulmonary hypertension, increased nitrogen dioxide levels (a lung irritant), and methemoglobinemia. However, due to the short duration of delivery in this study, it is unlikely these events will occur.

This study will test the hypothesis that a combination of inhaled nitric oxide and oxygen is more sensitive than 100% supplemental oxygen alone in detecting pulmonary vasoreactivity in patients with pulmonary hypertension.

8. STUDY OBJECTIVES

The primary objective of the trial is to compare the number of patients with reversible pulmonary hypertension (vasoreactivity) due to nitric oxide for inhalation and oxygen as compared to 100% oxygen. The criteria for response are:

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%)

The additional objectives of the trial are to compare the incidence and types of drug related and serious adverse events as well as the number of patients with reversible pulmonary hypertension due to nitric oxide for inhalation alone compared to 100% oxygen and to oxygen with nitric oxide for inhalation.

9. INVESTIGATIONAL PLAN

9.1 Overall Study Plan and Design

This trial will be an open, prospective, multi-center, randomized, controlled trial that will compare the utility and side effects of oxygen, nitric oxide and a combination of nitric oxide and O_2 in determining pulmonary reactivity. Each patient will be screened for enrollment and fulfill all entry criteria described in section 9.3. Upon obtaining informed consent approved by the institution's IRB/IEC, patients will be randomly assigned, using a randomization table, to receive either nitric oxide for inhalation at 80 ppm or 100% O_2 as their initial dose. The patients will either be under general anesthesia or awake sedation (mild sedation). Once the study drug delivery equipment is prepared, baseline data will be collected. Using a calibrated INOvent®, either nitric oxide for inhalation at 80 ppm or 100% O_2 will be continuously administered to the patient for ten minutes followed by data collection. The second dose will be the same as the first dose with the addition of either 80 ppm nitric oxide for patients receiving O_2, or 100% O_2 for patients receiving nitric oxide. This dose of 80 ppm NO and 100% O_2 will be delivered for ten minutes followed by data collection. There will be a ten-minute wash out period following this administration. Baseline data will again be collected followed by a ten minute administration of either 80 ppm nitric oxide or 100% O_2. The study drug delivered for this third administration will be the one that was not randomly assigned for the initial study drug administration.

For each patient, NO_2 levels will be monitored throughout the treatment period. Treatment with study gas will be discontinued if NO_2 levels exceed 3 ppm. Treatment can also be discontinued at the discretion of the attending physician or following the presentation of an adverse response to study drug. All adverse reactions will be recorded while on study gas. Serious adverse events will continue to be recorded during the treatment period through day 1 or discharge from the hospital, whichever comes first. Qualification and reporting of all serious adverse events will occur as per the Code of Federal Regulations (CFR) and ICH guidelines.

One appointed clinical staff member at each site will be responsible for the set up and use of the treatment gas delivery system. This individual may also be responsible for maintaining drug accountability records for the sponsor.
Following the acute diagnostic procedure, a brief follow up contact will be made on each patient to determine the vital status 1 year after the diagnostic procedure.

9.2 Discussion of Study Design

This is an open, randomized, prospective, multi-center, controlled trial to demonstrate which diagnostic treatment is most capable of identifying patients with a reactive pulmonary vascular bed. Each patient will serve as his/her own control, receiving all three treatment regimens: 80 ppm nitric oxide for inhalation, 80 ppm nitric oxide and 100% O_2, and the comparison treatment, 100% O_2. Due to the short half-life of NO, a 10 minute washout period following the nitric oxide for inhalation and 100% O_2 treatment will allow sufficient time for elimination of the drug effect before the administration of the comparison treatment.

9.3 Selection of Study Population

The expected population to be enrolled in this study will include patients with Idiopathic Pulmonary Arterial Hypertension, CHD (with or without intravascular shunt) with pulmonary hypertension, and cardiomyopathies. Patients will be stratified based on entry diagnosis. Patients who are either under general anesthesia or awake sedation will be included.

9.3.1 Inclusion Criteria

The patient must meet the following criteria:

1. Have any one of the three disease categories:
    a. Idiopathic Pulmonary Arterial Hypertension
        i. PAPm › 25mmHg at rest, PCWP ≤ 15mmHg, and PVRI › 3 u· m^2 or diagnosed clinically with no previous catheterization.
    b. CHD with pulmonary hypertension repaired and unrepaired,
        i. PAPm › 25mmHg at rest, and PVRI › 3 u· m^2 or diagnosed clinically with no previous catheterization

c. Cardiomyopathy

i. PAPm › 25mmHg at rest, and PVRI › 3 u•m^2 or diagnosed clinically with no previous catheterization.

2. Scheduled to undergo right heart catheterization to assess pulmonary vasoreactivity by acute pulmonary vasodilation testing.
3. Males or females, ages 4 weeks to 18 years, inclusive
4. Signed IRB/IEC approved informed consent (and assent if applicable).

9.3.2 Exclusion Criteria

The patient will be excluded from enrollment if any of the following are true:

1. Focal pulmonary infiltrates on chest radiograph.
2. Diagnosed with severe obstructive or restrictive pulmonary disease that is significantly contributing to the patient's pulmonary hypertension.
3. Received treatment with nitric oxide for inhalation within 30 days prior to study initiation, are on other investigational medications, nitroglycerin, sodium nitroprusside, sildenafil, other PDE-5 inhibitors, or prostacyclin.
4. Pregnant (urine HCG +).
5. Baseline PCWP > 20 mmHg

9.3.3 Removal of Patients from Therapy or Assessment

Study gas will be discontinued if NO_2 levels exceed 3 ppm. Alarms on the INOvent® exist to alert clinical personnel when NO_2 levels > 3 ppm. Treatment may also be discontinued if the patient (or legal representative) withdraws their consent or the investigator deems it in the best medical interest of the patient.

9.4 Treatments

9.4.1 Treatments Administered

After obtaining a signed informed consent form, each patient will receive either nitric oxide for inhalation administered using an INOvent® delivery system, or 100% O_2. The INOvent® is designed to add nitric oxide at preset levels to a ventilator circuit so that inspired NO concentrations remain unchanged despite changes in ventilation modes.

- Patients who are under general anesthesia will be intubated and receive nitric oxide for inhalation, 100% O_2 or a combination of NO and O_2. The NO will be administered using an INOvent® delivery system through a t-connector downstream of the inspiratory limb of a mechanical ventilator.
- Patients who are under awake sedation (mild sedation) will receive nitric oxide for inhalation, 100% O_2 or a combination of NO and O_2. The NO will be administered using an INOvent® delivery system through a properly fitted, sealed facemask.

Each patient will be randomized as to which study drug (80 ppm NO or 100%O_2) they will receive as the initial dose. The second dose administration will be 80ppm NO for inhalation with 100% O_2 (set - approximate oxygen delivery 90%) and the third dose administration will be whichever study drug was not initially administered (NO or 100% O_2). There will be a ten-minute wash out period between the second and third dose administration.

9.4.2 Identity of Investigational Product

The active drug, nitric oxide for inhalation, will be manufactured by INO Therapeutics. Nitric oxide for inhalation will be supplied in size "88" US or "10L" EU, aluminum cylinders at a concentration of 800 ppm, balance nitrogen (99.92% grade 5 nitrogen, 0.08% pharmaceutical grade nitric oxide). The cylinders should be stored in a controlled, limited access area at standard room temperature. Cylinders labels will distinguish among sites but will not be pre-assigned patient numbers. The oxygen used in this study will be provided by each hospital.

9.4.3 Method of Assigning Patients to Treatment Groups

Randomization of the initial study administered will be a block randomization by site. Only the first treatment assignment will be randomized. The randomization codes will be provided to sites in individual envelopes per patient. Patients will be serving as their own control and will receive all three treatments.

9.4.4 Selection of Doses in the Study

While varying doses of NO for inhalation have been shown to be safe and effective in decreasing PAPm and PVRI, the use of 80 ppm may elicit a response in a small percentage of the non-responders to lower doses. (Wessel D, personal communication, [redacted]) Therefore, 80 ppm of NO for inhalation will be used in an effort to capture data from the maximum number of potential responders. Previous short duration studies with 80 ppm nitric oxide for inhalation have shown no significant increase in the levels of methemoglobin.[7,8]

9.4.5 Selection and Timing of Dose for Each Patient

Once informed consent is obtained, the delivery equipment will be set up with the appropriate study drug cylinders. Doses of 80 ppm NO for inhalation, 100% supplemental O_2 and 80 ppm NO for inhalation with 100% O_2 (set - approximate oxygen delivery 90%) will be administered for at least 10 minutes. The order of the initial treatment will be randomized. The second dose administered will always be 80 ppm NO for inhalation with 100% O_2 followed by a ten minute wash out period. The third dose will be the treatment that was not randomly assigned for the initial study drug administration.

9.4.6 Treatment Group Assignment Blinding

Treatment will not be blinded. Prior to initial baseline measurements, the cardiac catheter will be placed and the drug delivery equipment prepared. The lack of a placebo and the nature of the data being collected (e.g. hemodynamic variables) are expected to be sufficiently objective to eliminate investigator bias.

9.4.7 Prior and Concomitant Therapy

Patients who have received treatment with nitric oxide for inhalation within 30 days prior to study initiation, other investigational medications, nitroglycerin, sodium nitroprusside, sildenafil or other PDE-5 inhibitors or prostacyclin are excluded from this trial.

Ketamine should not be used as part of the anaesthetic regimen.

Concomitant medications are to be recorded on the case report form.

9.4.8 Treatment Compliance

It is the principal investigator's responsibility to ensure that the treatment, as detailed in the approved protocol, is administered to each enrolled patient. The investigator must administer the drug only to patients under the investigator's (or responsible sub-investigator) direct supervision. All drug used in the study must be accounted for and documented in a usage log provided by the sponsor.

9.5 Efficacy and Safety Variables

9.5.1 Efficacy and Safety Schedule of Assessments

The measurements to be obtained and recorded to measure efficacy and safety are shown in Table 1. The schedule of treatments to be administered is shown in Table 2.

Table 1. Schedule of Assessments

Assessment	Screen	Baseline (Room Air or BL 02)	Study Drug Start	Treatment 1 80 ppm NO or 100% O_2	Treatment 2 80 ppm NO and 100% O_2	Wash Out Period	Baseline-2	Treatment 3 80 ppm NO or 100% O_2
Informed Consent	X							
Demography		X						
Hemoglobin		X						
Hemodynamic[1] Measurements		X		X	X		X	X
Adverse Events[2]				<X>				
Serious Adverse Events[3]				<X>				
Oxygen Consumption		X						
Arterial pH		X						X

[1] Hemodynamic measurements: HR, SAP, DAP, MAP, CVPm, PAPs, PAPd, PAPm, PAWPm and CO
[2] Adverse events are to be collected until patient is discontinued from study gas.
[3] Serious adverse events are to be collected through 12 hours after discontinuation of study gas, or discharge, whichever comes first.
Follow up assessment at 1 and 3 years. will consist of telephone call to assess medical therapies or surgical procedures pertaining to pulmonary/cardiac disease, and vital status /date of death if applicable.

Table 2. Schedule of Treatments

	Treatment	Hemodynamic Measurements	Cardiac Output	End of Study Treatment
Baseline 1-Data Collection	Baseline $O_{2\ or}$ Room Air*	X	X	
10 Minute Dose	**80ppm NO or 100% O_2			
Data Collection		X	X	X
10 Minute Dose	NO + 100% O_2			
Data Collection		X	X	X
10 Minute Washout				
Baseline 2-Data Collection	Baseline $O_{2\ or}$ Room Air	X	X	
10 Minute Dose	*80ppm NO or 100% O_2			
Data Collection		X	X	X

*Baseline assessments should be made with the patient breathing room air, whenever possible.
**Randomized: Patients will be randomized to as to which treatment is received first.

9.5.2 Data Collection

Baseline Measurements

1. Compliance with the inclusion/exclusion criteria will be documented.
2. Demographic information will be recorded.
3. Diagnosis (underlying disease) will be noted.
4. Concomitant medications will be recorded.
5. Hemoglobin (Hgb)-(value may be within one week of baseline)
6. arterial pH
7. Hemodynamic Measurements:
   (1) Heart Rate (HR)
   (2) Systolic blood pressure (SAP)
   (3) Diastolic blood pressure (DAP)
   (4) Mean arterial pressure (MAP)
   (5) Mean central venous pressure (CVPm)
   (6) Systolic pulmonary artery pressure (PAPs)
   (7) Diastolic pulmonary artery pressure (PAPd)
   (8) Mean pulmonary artery pressure (PAPm)

(9) Mean pulmonary artery wedge pressure (PAWPm) (or directly measured LA pressure, when accessible)

(10) Cardiac output (CO). Cardiac output will be obtained by either the Fick (collections include: VO_2, PaO_2, SaO_2, PA Sat, SvO_2 and PV Sat) or Thermal Dilution method. The case report form will capture which method of determining the cardiac output was used.

Measurements Following First Treatment Administration

1. Hemodynamic Measurements (HR, SAP, DAP, MAP, CVPm, PAPs, PAPd, PAPm, PAWPm, and CO)
2. Adverse events are to be collected until patient is discontinued from study gas.
3. Serious adverse events will be collected through study day 1 or discharge, whichever comes first.

Measurements Following Second Treatment Administration

- Hemodynamic Measurements (HR, SAP, DAP, MAP, CVPm, PAPs, PAPd, PAPm, PAWPm, and CO)

Measurements Following Third Treatment Administration

- Hemodynamic Measurements (HR, SAP, DAP, MAP, CVPm, PAPs, PAPd, PAPm, PAWPm, and CO)
- Arterial pH

Measurements 1 year and 3 years after the diagnostic procedure

- Therapies received since the diagnostic procedure
- Date of surgery (if any)
- Vital status and date of death, if applicable

Procedures for Maintenance of Baseline Oxygen Saturation Levels

Adjustments will need to be made to maintain the patients baseline oxygen saturation level and to avoid the administration of a hypoxic gas mixture. This should be done before and after each treatment.

Awake Sedation Patients

Patients Not on Supplemental O_2

1. Right heart catheterization.
2. Place properly fitted, sealed facemask on patient (check for leaks).
3. Using 21% oxygen, adjust flow to 15 L/min.
4. Allow for a 10-minute equilibrium period.
5. Take baseline hemodynamic measurements.
6. Note patient's SpO_2 reading and analyzed O_2 reading (INOvent monitor).
7. Start treatment (80 ppm NO or 100% O_2 as per randomization table).
8. After 1 minute, adjust oxygen blender to maintain the patient's baseline analyzed O_2 reading. For the nitric oxide for inhalation treatment, expect a 10% decrease in the patient's FiO_2. During this treatment, you may adjust the blender setting by 10% so as to maintain the baseline O_2 reading.
9. Maintain treatment for 10 minutes.
10. Take hemodynamic measurements.
11. Start second treatment by adding either 80 ppm NO or 100% O_2 so that the administered treatment is a combination of 80 ppm NO and 100% O_2.
12. Maintain treatment for 10 minutes.
13. Take hemodynamic measurements.
14. Stop treatment but do not remove facemask until completion of the study.
15. Adjust oxygen blender to maintain monitored FiO_2 reading of 21%.
16. Do not remove facemask (The facemask will remain in place during the entire procedure. Although it may be loosened during the wash out periods to maintain patient comfort).
17. 10 minute wash out period.
18. Take baseline hemodynamic measurements
19. Start third treatment of either 80 ppm NO or 100% O_2. The third treatment will be whichever study gas was not administered during the first treatment period.
20. Maintain treatment for 10 minutes.

21. Take hemodynamic measurements.
22. Stop treatment.
23. Adjust oxygen blender to maintain monitored FiO_2 reading of 21%.
24. Allow for a ten-minute equilibrium period.
25. Remove facemask from patient.

Patients on Supplemental O_2

1. Obtain patients baseline oxygen saturation levels (pulse oximetry) with patient's supplemental oxygen in place.
2. Right heart catheterization
3. Place properly fitted, sealed face mask on patient (check for leaks)
4. Adjust the patient's O_2 to match delivery they were receiving through nasal cannula prior to study enrollment using the following conversion table as a guide (or titrate FiO_2 to maintain baseline SpO_2):

L/min	0	1	2	3	4	5	6
O_2 (%)	21	25	29	33	37	41	45

5. Re-check patient's O_2 saturation level. It should be the same as initial value, if not, adjust the blender accordingly.
6. Note analyzed O_2 reading from INOvent.
7. Allow for a 10-minute equilibrium period.
8. Take baseline hemodynamic measurements.
9. Start treatment (80 ppm NO or 100% O_2 as per randomization table).
10. After 1 minute adjust the oxygen blender to maintain the baseline SpO_2.
11. Note analyzed O_2 reading from INOvent.
12. Maintain treatment for 10 minutes.
13. Take hemodynamic measurements.
14. Start second treatment by adding either 80 ppm NO or 100% O_2 so that the administered treatment is a combination of 80 ppm NO and 100% O_2.
15. Maintain treatment for 10 minutes.
16. After 1 minute adjust the oxygen blender to maintain the baseline SpO_2.
17. Take hemodynamic measurements
18. Stop treatment but do not remove facemask until completion of study.

19. Adjust oxygen blender to maintain baseline SpO_2
20. Do not remove facemask (The facemask will remain in place during the entire procedure. Although it may be loosened during the wash out periods to maintain patient comfort)
21. 10 minute wash out period
22. Take baseline hemodynamic measurements
23. Start third treatment of either 80 ppm NO or 100% O_2. The third treatment will be whichever study gas was not administered during the first treatment period.
24. After 1 minute adjust oxygen blender to maintain baseline SpO_2.
25. Take hemodynamic measurements.
26. Stop treatment.
27. Adjust oxygen blender to maintain baseline SpO_2.
28. Allow for a ten-minute equilibrium period.
29. Remove facemask.
30. Put patient back on nasal cannula administration of supplemental O_2.

Patients Intubated and Under General Anesthesia

Patients Not on Supplemental O_2

1. Patients will be placed under general anesthesia and intubated according to the standard medical care and procedures of the institution.
2. Right heart catheterization.
3. Using 21% oxygen, adjust flow to 15 L/min.
4. Allow for a 10-minute equilibrium period.
5. Take baseline hemodynamic measurements.
6. Note patient's SpO_2 reading and analyzed O_2 reading (INOvent monitor).
7. Start treatment (80 ppm NO or 100% O_2 as per randomization table).
8. After 1 minute, adjust oxygen blender to maintain the patient's baseline analyzed O_2 reading. For the nitric oxide for inhalation treatment, expect a 10% decrease in the patient's FiO_2. During this treatment, you may adjust the blender setting by 10% so as to maintain the baseline O_2 reading.
9. Maintain treatment for 10 minutes.
10. Take hemodynamic measurements.
11. Start second treatment by adding either 80 ppm NO or 100% O_2 so that the administered treatment is a combination of 80 ppm NO and 100% O_2.

12. After 1 minute, adjust oxygen blender to maintain the patient's baseline analyzed O_2 reading.
13. Maintain treatment for 10 minutes.
14. Take hemodynamic measurements.
15. Stop treatment.
16. Adjust oxygen blender to maintain monitored FiO_2 reading of 21%.
17. 10 minute wash out period.
18. Take baseline hemodynamic measurements
19. Start third treatment of either 80 ppm NO or 100% O_2. The third treatment will be whichever study gas was not administered during the first treatment period.
20. After 1 minute, adjust oxygen blender to maintain the patient's baseline analyzed O_2 reading.
21. Maintain treatment for 10 minutes.
22. Take hemodynamic measurements.
23. Stop treatment.
24. Adjust oxygen blender to maintain monitored FiO_2 reading of 21%.
25. Extubation will occur according to each institution's standard of care.

Patients on Supplemental O_2

1. Before intubation and initiation of general anesthesia, obtain patients baseline oxygen saturation levels (pulse oximetry) with patient's supplemental oxygen in place.
2. Patients will be placed under general anesthesia and intubated according to the standard medical care and procedures of the institution.
3. Right heart catheterization
4. Adjust the patient's O_2 to match delivery they were receiving through nasal cannula prior to study enrollment.

2. Re-check patient's O_2 saturation level. It should be the same as initial value, if not, adjust the blender accordingly.
3. Note analyzed O_2 reading from INOvent.
4. Allow for a 10-minute equilibrium period.

7. Take baseline hemodynamic measurements.
8. Start first treatment (80 ppm or 100% O_2 as per randomization table).
9. After 1 minute adjust oxygen blender to maintain baseline SpO_2.

10. Maintain treatment for 10 minutes.
11. Take hemodynamic measurements.
12. Start second treatment by adding either 80 ppm NO or 100% O_2 so that the administered treatment is a combination of 80 ppm NO and 100% O_2.
13. After 1 minute adjust oxygen blender to maintain baseline SpO_2.
14. Maintain treatment for 10 minutes.
15. Take hemodynamic measurements.
16. Stop treatment.
17. Adjust oxygen blender to maintain patient's baseline SpO_2.
18. Ten minute wash out period
19. Take baseline hemodynamic measurements
20. Start third treatment of either 80 ppm NO or 100% O_2. The third treatment will be whichever study gas was not administered during the first treatment period.
21. Adjust oxygen blender to maintain patient's baseline SpO_2.
22. Maintain treatment for 10 minutes.
23. Take hemodynamic measurement.
24. Stop treatment.
25. Adjust oxygen blender to maintain patient's baseline SpO_2.
26. Allow for a ten-minute equilibrium period.
27. Extubation will occur as per each institutions standard of care.

9.5.3 Ventilator Weaning and Extubation Strategy

Following the third treatment administration, study patients under general anesthesia will be weaned from mechanical ventilator and extubated according to standard medical care and hospital specific protocol. Study patients under 'awake sedation' will have the treatments discontinued and facemask removed according to standard medical care and hospital specific protocol.

9.5.4 Appropriateness of Measurements

Demographic and baseline data will be collected and evaluated in an attempt to demonstrate that the treatment groups are well balanced with respect to age, sex, race,

and that there were no substantial differences in either population with regards to the underlying disease. The measured and calculated values in this protocol are used in standard clinical practice to assess pulmonary vasoreactivity. Both the PAPm and the PVRI have been shown to be useful parameters in measuring the body's response to vasoactive drug therapy.

9.5.5 Efficacy Variables

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 $\geq$ 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 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 and 3 years, by response

9.5.6 Safety Variables

The following safety variables will be assessed throughout the treatment gas administration period:

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

9.5.7 Drug Concentration Measurements

The INOvent® gas delivery system measures the flow of gas in the ventilator circuit and a mass flow controller adds NO to the ventilator gas flow to create the desired concentration. The device continuously samples gas from the side port adapter and measures oxygen, nitric oxide and nitrogen dioxide with electrochemical monitors.

9.6 Data Quality Assurance

Prior to study initiation there will be meetings to prepare investigators and standardize performance at each study center associated with the trial. Data will be collected by the study site coordinator and verified at the site by the clinical research associate (CRA). This data will be monitored and verified 100% to the medical charts. Data will be double key entered into a validated Oracle Clinical database managed by the Sponsor. Discrepancies will be flagged and the database manager will make the decisions regarding the flags. The trial staff at the hospital will make data corrections as necessary

9.7 Statistical Methods Planned and Determination of the Sample Size

See Appendix 2.

9.7.1 Sample Size Determination

The following assumptions are made:

1. The desired type I (α) error of 0.05 is the threshold for statistical significance (2-tailed)

2. The expected percentage of patients who have a reduction in PVR of ≥ 20% using 80 ppm NO and 100% O_2 and will have a reduction in PVR of ≤ 20% using 100% O_2 will be 24%.[7]
3. The expected percentage of patients who have a reduction in PVR of ≥ 20% using 100% O_2 and will have a reduction in PVR of ≤ 20% using 80 ppm NO and 100% O_2 will be 0%.[7]
4. The desired power (1 - ß) for the trial is 80%.

Enrollment will proceed until at least 150 patients have been enrolled in the trial.

9.7.2 Interim Analysis

No interim analysis is planned for this trial.

9.8 Changes in Conduct of the Study or Planned Analyses

Any change in the conduct of the study or planned analyses instituted after the start of the study will be documented. The time and reason for the change, the procedure used to decide on the change, the person or group responsible for the change and the nature and content of the data available when the change is made will be documented whether or not the change was documented as a formal protocol amendment.

10. ADMINISTRATIVE DETAILS

10.1 Accountability of Study Drug and Equipment

Drug receipt, return and usage logs for the clinical supplies must be maintained by the investigator at the study site to assure accountability of all gas cylinders supplied. This documentation must include the patient number, cylinder serial number, date the treatment gas was received, date the gas was dispensed, amount used, amount remaining in stock, and date treatment gas was returned. The documents will be reviewed at each monitoring visit.

It is prohibited to use drugs or medical devices supplied by INO Therapeutics specifically for use in this protocol for patients not enrolled in this protocol.

10.2 Case Report Forms

All case report forms are to be completed within one month after patient completion of the study. A case report form is provided for each patient. All forms are to be filled out in black ink or typed.

Correction(s) of data on the case report form should be made by crossing out the incorrect data (in a manner that leaves the previous entry identifiable) and writing the correct values next to those crossed out. Each correction must be initialed and dated by the individual making the correction.

10.3 Investigator Requirements

Prior to study initiation, the investigator will complete and submit to INO Therapeutics LLC all documents required by the FDA 21 CFR Part 50, 56, and 312 and ICH GCP (E6) section 8.0. Additionally, each investigator must assure the following:

- An Institutional Review Board (IRB) / Independent Ethics Committee (IEC) that complies with the requirements set forth in 21 CFR Part 50 and 56 of FDA regulations or ICH GCP (E6) section 3.0 will be responsible for the initial and continuing review and approval of the proposed clinical study.

- Prompt reporting to the IRB / IEC all changes in research activity and all unanticipated problems involving risks to human patients or others, and that he/she will not make any changes in the research until the IRB / IEC has approved the changes and INO Therapeutics, LLC has notified the FDA and/or appropriate regulatory agency, as required by 21 CFR 56 and 312.30 or ICH GCP (E6) section 4.5 and 4.10. Documentation of approval must be forwarded to INO Therapeutics for any amendment requiring IRB/IEC approval.
- Reporting to IRB/IEC at least yearly on the progress of the investigation and within three months after completion, termination or discontinuation of the study.
- Ongoing evaluation, management and reporting of adverse experiences.
- Submission of a Financial Interest Disclosure statement detailing all financial involvement with the Sponsor (including other research grants, stock, consultation fees, etc.) as required by 21 CFR 54.

10.4 Recording of Adverse Events

Each patient will be assessed for any new or continuing adverse events by the clinical investigator and the study coordinator. An adverse event is defined as any untoward medical occurrence in a patient/subject of a clinical investigation that involves the administration of a pharmaceutical product. The event need not have a causal relationship with the treatment. This includes any events that are not seen at baseline or, if present at baseline, have worsened in severity. Any adverse event reported by the caregiver or noted by the investigator or study coordinator will be recorded on the Adverse Event pages on the case report form. The severity and drug relationship will be determined, and any management required will be recorded. The adverse event will be followed until resolution or discontinuation of the study drug, whichever occurs first. The investigator will review the clinical laboratory test results in a timely fashion. Only those results qualifying as adverse events, as defined above, will be recorded on the Adverse Event section of the case report form.

10.4.1 Study Drug Relationship

The investigator is responsible for assessing the causal relationship between any events and the study treatment. Additionally, the investigator is responsible for providing appropriate treatment for the event and for adequately following the event until resolution. The clinical investigator should determine the study drug relationship using the following explanations:

Not Related

The event is clearly related to other factors such as the patient's/subject's clinical state, therapeutic interventions, or concomitant drugs administered to the patient/subject.

Remote

The event was most likely produced by other factors such as the patient's/subject's clinical state, therapeutic interventions or concomitant drugs administered to the patient/subject, and does not follow a known response pattern to the study drug.

Possible

The event follows a reasonable temporal sequence from the time of drug administration and/or follows a known response pattern to the study drug, but could have been produced by other factors such as the patient's/subject's clinical state, therapeutic interventions or concomitant drugs administered to the patient/subject.

Probable

The event follows a reasonable temporal sequence from the time of drug administration and follows a known response pattern to the study drug and cannot be reasonably explained by other factors such as the patient's/subject's clinical state, therapeutic interventions or concomitant drugs administered to the patient/subject.

Highly Probable

The event follows a reasonable temporal sequence from the time of drug administration and follows a known response pattern to the study drug and cannot be reasonably explained by other factors such as the patient's/subject's clinical state, therapeutic interventions or concomitant drugs administered to the patient/subject and either occurs immediately following study drug administration, or improves on stopping the drug, or reappears on repeat exposure, or there is a positive reaction at the application site.

Temporal sequence is defined as an association between the suspect drug and the observed reaction or event in which the suspect drug was present prior to the reaction or event as defined by history or blood level of drug.

Study drug(s) includes the drug(s) under evaluation, the reference drug(s), placebo, or any other drug(s) required by the protocol.

Severity of an adverse event will be defined from the qualitative assessment of the degree of intensity of the event as determined by the investigator or as reported to him/her by the patient/subject. The assessment of severity is made irrespective of drug relationship or seriousness of the event and should be evaluated according to the following scales:

1 = **Mild** - awareness of the symptom but easily tolerated

2 = **Moderate** - discomfort enough to interfere with normal activities

3 = **Severe** - Incapacitating with the inability to perform normal activities

10.4.2 Serious Adverse Events

A serious adverse event is defined as any event that at any dose: results in death, is life-threatening, results in persistent or significant disability / incapacity, requires or prolongs inpatient hospitalization, or is a congenital anomaly. Important medical events that without medical or surgical intervention would also have resulted in one of the outcomes listed above are also considered a serious adverse event All serious adverse events occurring during the study, and within 12 hours of the discontinuation of treatment gas, or hospital discharge whichever comes first, must be reported to INO Therapeutics within 24 hours by fax/telephone to:

Catherine Evans

INO Therapeutics Regulatory Affairs Associate

Phone: +001 908 238-6655

Fax: +001 908 238-6635

If you have specific questions regarding an adverse event being classified as serious, you may contact the Medical Monitor for this study:

James S. Baldassarre, MD

INO Therapeutics Senior Director of Research & Development

Phone: +001 908 238-6363

Cell: +001 908 500-8111

The patient/subject must be monitored carefully until the condition resolves, reaches a clinically stable endpoint and/or the etiology is identified. The initial telephone contact will be followed within 24 hours by completing an SAE packet with detailed descriptions of the event and supported as needed with written copies of hospital case reports, autopsy reports, and other documents when applicable.

All serious and unexpected adverse events must be reported to the IRB/IEC and appropriate local regulatory agency in writing.

10.4.3 Unexpected Adverse Events

An unexpected adverse event is any event that is not identified in nature, severity or frequency in the current investigator's brochure.

10.5 Records Retention

In compliance with GCPs and both U.S. Federal law and ICH guidelines, copies of all records (e.g., informed consent documents, laboratory data slips, source documents, IND safety reports, test article dispensing records, etc.) which support case report forms of this study, must be retained in the files of the responsible investigator for a minimum of two years following notification by INO Therapeutics that all investigations at all sites are completed, terminated, or discontinued, or that the Food and Drug Administration or other appropriate regulatory agency has approved the New Drug Application. If the investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the

responsibility. INO Therapeutics, LLC. must be notified in writing of the name and address of the new custodian.

10.6 Monitoring and Audits

The study will be periodically monitored/audited by a representative of INO Therapeutics, LLC It is the responsibility of the principal investigator to provide all study records, including case report forms, source documentation, etc., to the monitor at their visit.

The United States Food and Drug Administration, in the person of a scientifically trained and properly authorized employee of the Agency, or a representative of the local regulatory agency may request access to all study records, including source documents, for inspection and copying.

10.7 Amendments to the Protocol

Neither the investigator nor INO Therapeutics, LLC will amend or modify the protocol without written notification of the other. All amendments must be approved by INO Therapeutics prior to implementation. All amendments must be submitted to the to the IRB/IEC as required. The IRB/IEC must approve major amendments prior to implementation at the study site.

10.8 Termination of Trial

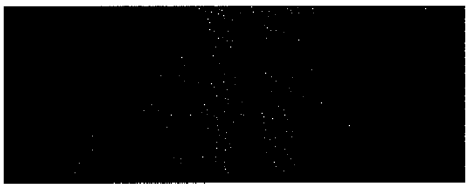
It is agreed that, for reasonable cause, either the investigator or the sponsor, INO Therapeutics, LLC may terminate this study, provided written notice is submitted at a reasonable time in advance of intended termination.

11. REFERENCE LIST

1. Christman BW, McPherson CD, Newman JH, King GA, Bernard GR, Groves BM, Loyd JE. An imbalance between the excretion of thromboxane and prostacyclin metabolites in pulmonary hypertension. *N Engl J Med* 1992; 327:70-75.
2. Giaid A, Saleh D. Reduced expression of endothelial nitric oxide synthase in the lungs of patients with pulmonary hypertension. *N Engl J Med* 1995; 333:214-221.
3. Giaid A, Yanagisawa M, Langleben D, et al. Expression of endothelin-1 in the lungs of patients with pulmonary hypertension. *N Engl J Med* 1993; 328:1732-1739.
4. Rossaint R, Falke KJ, Lopez F, et al. Inhaled nitric oxide for the adult respiratory distress syndrome. *N Engl J Med* 1993; 328:399-405.
5. Adatia I, Thompson J, Landzberg M, et al. Inhaled nitric oxide in chronic obstructive lung disease. *Lancet* 1993; 341:307-308.
6. Kinsella JP, Neish SR, et al. Low dose inhalational nitric oxide in persistent pulmonary hypertension of the newborn. *Lancet* 1992; 340:819-820.
7. Atz AM, Adatia I, Lock JE, Wessel DL. Combined effects of nitric oxide and oxygen during acute pulmonary vasodilator testing. *J Am Coll Cardiol* 1999; 33(3): 813-9.
8. Dellinger RP, Zimmerman JL, Taylor RW, Straube RC, et al. Effects of inhaled nitric oxide in patients with acute respiratory distress syndrome: Results of a randomized phase II trial. *Crit Care Med* 1998; 26:15-23
9. Chatterjee K, De Marco T, et al. Pulmonary Hypertension: Hemodynamic Diagnosis and Management. *Arch Intern Med* 2002; 162:1925-1933

APPENDIX 1. PROTOCOL VERSIONS

Protocol Versions:



APPENDIX 2. ANALYTIC PLAN

A. Analysis Populations

All efficacy and safety analyses will be done on all patients randomized (an intent-to-treat basis). If the non-evaluable proportion of patients exceeds 5%, then the efficacy analyses will also be performed on the evaluable patients.

Evaluable patients are patients who meet all entry criteria, receive any treatment gas, and have the data available to calculate the efficacy variables.

Intent-to-treat patients will be all patients randomized regardless of actual receipt of treatment gas, the treatment gas actually received, or the appropriateness of their enrollment.

B. Analyses of Baseline Characteristics

Allowing for the fact that all patients will be randomly assigned to each treatment group, any discrepancies in the distributions of baseline characteristics should be considered as random occurrences. However, the distributions of all baseline characteristics (age, sex, race, etc.) will be compared between the two treatment groups.

C. Primary Efficacy Analysis

The primary efficacy variable for this trial is the number of patients that meet response criteria. A positive response is defined 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%)

These variables will be calculated as follows:

% Change in PAPm from Baseline =

$((PAPm_{Treatment} - PAPm_{Baseline}) / PAPm_{Baseline}) \times 100$

% Change in PVRI from Baseline =

$((PVRI_{Treatment} - PVRI_{Baseline}) / PVRI_{Baseline}) \times 100$

All patients not meeting the above criteria will be counted as having a negative response.

It is hypothesized that the number of patients receiving a combination of NO and O_2 who have a positive response will be significantly greater than the number of patients receiving O_2 alone. The null hypothesis is therefore formerly expressed as:

H_o: There is no difference in the number patients with a positive response in PAPm or PVRI between the NO and O_2 group versus the O_2 alone group.

The alternative hypothesis is:

H_a: A difference exists in the number patients with a positive response in PAPm or PVRI between the NO and O_2 group versus the O_2 alone group.

The difference in the primary efficacy variable(s) between the two treatment groups will be tested using the McNemar Test for Significance of Changes. This test will be conducted with the type I (α) error of 0.05 for statistical significance (2-tailed).

D. Secondary Efficacy Analysis

All tests will be conducted with the type I (α) error of 0.05 for statistical significance (2-tailed).

Number of Patients Who Meet Response Criteria in the NO Group vs. the O_2 Group

This analysis is identical to that outlined the section C of this analytic plan with the exception of the two treatments that will be compared. It is hypothesized that the number of patients receiving NO alone who have a positive response will be significantly greater than the number of patients receiving O_2 alone. The null hypothesis is therefore formerly expressed as:

***H_o*:** There is no difference in the number patients with a positive response between the NO group versus the O_2 alone group.

The alternative hypothesis is:

***H_a*:** A difference exists in the number patients with a positive response between the NO group versus the O_2 alone group.

The difference between the two treatment groups will be tested using the McNemar Test for Significance of Changes. This test will be conducted with the type I (α) error of 0.05 for statistical significance (2-tailed).

Number of Patients Who Meet Response Criteria in the NO Group vs. the NO + O_2 Group

This analysis is also identical to that outlined the section C of this analytic plan with the exception of the two treatments that will be compared. It is hypothesized that the number of patients receiving NO alone who have a positive response will be significantly greater than the number of patients receiving NO + O_2. The null hypothesis is therefore formerly expressed as:

***H_o*:** There is no difference in the number patients with a positive response between the NO group versus the NO + O_2 group.

The alternative hypothesis is:

***H_a*:** A difference exists in the number patients with a positive response between the NO group versus the NO + O_2 group.

The difference between the two treatment groups will be tested using the McNemar Test for Significance of Changes. This test will be conducted with the type I (α) error of 0.05 for statistical significance (2-tailed).

Differences in PVR, PAPm and Cardiac Output in Room Air vs. Each Treatment Group

It is hypothesized that there is a difference in PVRI and PAPm readings between room air (baseline) and each treatment group. The hypotheses are formerly expressed as:

H_o: There is no difference in PVRI between room air (baseline) and the NO + O_2 group.
The alternative hypothesis is:
H_a: A difference exists in PVRI between room air (baseline) versus the NO + O_2 group.

H_o: There is no difference in PVRI between room air (baseline) and the O_2 group.
The alternative hypothesis is:
H_a: A difference exists in PVRI between room air (baseline) versus the O_2 group.

H_o: There is no difference in PVRI between room air (baseline) and the NO group.
The alternative hypothesis is:
H_a: A difference exists in PVRI between room air (baseline) versus the NO group.

H_o: There is no difference in PAPm between room air (baseline) and the NO + O_2 group.
The alternative hypothesis is:
H_a: A difference exists in PAPm between room air (baseline) versus the NO + O_2 group.

H_o: There is no difference in PAPm between room air (baseline) and the O_2 group.
The alternative hypothesis is:
H_a: A difference exists in PAPm between room air (baseline) versus the O_2 group.

H_o: There is no difference in PAPm between room air (baseline) and the NO group.
The alternative hypothesis is:
H_a: A difference exists in PAPm between room air (baseline) versus the NO group.

H_o: There is no difference in cardiac output between room air (baseline) and the NO + O_2 group.
The alternative hypothesis is:
H_a: A difference exists in cardiac output between room air (baseline) versus the NO + O_2 group.

H_o: There is no difference in cardiac output between room air (baseline) and the O_2 group.
The alternative hypothesis is:
H_a: A difference exists in cardiac output between room air (baseline) versus the O_2 group.

H_o: There is no difference in cardiac output between room air (baseline) and the NO group.
The alternative hypothesis is:
H_a: A difference exists in cardiac output between room air (baseline) versus the NO group.

These hypotheses will be tested using the paired t-test if the normality assumption has not been violated, or the Wilcoxon Signed Ranks test if there is a violation of normality. All tests will be conducted with the type I (α) error of 0.05 for statistical significance (2-tailed).

Change in the Ratio of PA Pressure to Systemic Pressure

It is hypothesized that there is a difference in the ratio of PA pressure to systemic pressure between the NO and O_2 group versus the O_2 alone group. The hypotheses are formerly expressed as:

H_o: There is no difference in the ratio of PAPm to SAPm between the NO and O_2 group versus the O_2 alone group.
The alternative hypothesis is:
H_a: A difference exists in the ratio of PAPm to SAPm between the NO and O_2 group versus the O_2 alone group.

The difference in the ratios for each treatment group will be analyzed using an ANOVA model. The list of independent variables includes, but is not limited to, treatment, subject (nested within treatment sequence) and treatment sequence. Differences in treatment will be assessed with the type I (α) error of 0.05 for statistical significance (2-tailed).

Survival at 1 and 3 Years Following the Diagnostic Procedure

It is hypothesized that there is a difference in rates of survival at 1 and 3 years of those who met response criteria as outlined in section C of this analytic plan. The hypotheses are formerly expressed as:

H_o: There is no difference in the survival rate of patients with a positive response in PAPm or PVRI between the NO and O_2 group versus the O_2 alone group.
The alternative hypothesis is:
H_a: A difference exists in the survival rate of patients with a positive response in PAPm or PVRI between the NO and O_2 group versus the O_2 alone group.

The difference between the two treatment groups will be tested using the Fisher's Exact Test. This test will be conducted with the type I (α) error of 0.05 for statistical significance (2-tailed). In addition, a Kaplan-Meier plots will be generated for time to death for each treatment group.

E. Safety Analysis

Serious Adverse Events

The analysis will be performed on the number and types of serious adverse events reported in each treatment group. The incidence of all serious adverse events, stratified by MEDRA terms, MEDRA body system, and patients with specific serious adverse events will be tabulated. Additionally, the serious adverse events will be stratified by age, sex and race.

H_o: There is no difference in the number of reported serious adverse events between the NO, NO + O_2 and O_2 alone groups.

H_a: A difference exists in the number of reported serious adverse events between the NO, NO + O_2 and O_2 alone groups.

This comparison will be made using Cochran's Test for Related Observations.

Drug Related Adverse Events

The analysis will be performed on the number and types of drug related adverse events reported in each treatment group. The incidence of all drug related adverse events, stratified by MEDRA terms, MEDRA body system, and patients with specific adverse events will be tabulated. Additionally, the adverse events will be stratified by age, sex and race.

H_o: There is no difference in the number of reported drug related adverse events between the NO, NO + O_2 and O_2 alone groups.

H_a: A difference exists in the number of reported drug related adverse events between the NO, NO + O_2 and O_2 alone groups.

This comparison will be made using Cochran's Test for Related Observations.

F. Additional Analyses

All primary methods of analysis have been previously outlined in this document. However, INO Therapeutics reserves the right to perform any additional analyses deemed necessary according to any of the following reasons:

1. Any steering committee or medical monitor recommendations based on investigator concerns.
2. The presence of maldistributed baseline characteristics.
3. The administration of any medications thought to be affecting the treatment as determined by the steering committee and/or the medical monitor.

Additionally, several exploratory analyses will be conducted to determine the existence of any possible relationships between the response variables and diagnosis, delivery system, demographic criteria, etc. Due to the unknown nature of these analyses, INO Therapeutics, LLC declines to formalize the testing procedures in this analytic plan.

G. Interim Analyses

No interim analysis for efficacy or safety in this study is planned.

APPENDIX 3. LISTING OF AMENDMENT 1 CHANGES

AMENDMENT 1 CHANGES:

Cover Page, Version

Changed From:

"Original Protocol"

Changed To:

"Amendment 1"

Cover Page, Document Date

Changed From:

[redacted]

Changed To:

[redacted]

Cover Page, Study Contact

Deleted: Paul Bridges, European Regulatory Affairs

Changed From:

"Rebecca Light, Clinical Research Manager"

Changed To:

"Jodee Newman, Project Leader"

Synopsis

Changed From:
"Sponsor-INO Therapeutics, Inc."

Changed To:
"Sponsor-INO Therapeutics, LLC"

Changed From:
"Investigators-TBD"

Changed To:
"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 "

Changed From:
"Study Centers-TBD"

Changed To:
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

Secondary Endpoints-Addition:

4) Change in the ratio of PAPm to SAPm by treatment

5) Survival at 1 year by response

4. List of Abbreviations and Definitions of Terms

Addition:
Mean Systolic Arterial blood pressure

Page 19 Section 9.1

Addition:
"Following the acute diagnostic procedure, a brief follow up contact will be made on each patient to determine the vital status 1 year after the diagnostic procedure."

Section 9.5.1 Table 1 - Footnote

Addition:
Assessment-Baseline :Arterial pH
Follow up assessment at 1 yr. Will consist of telephone call to assess medical therapies or surgical procedures pertaining to pulmonary/cardiac disease, and vital status /date of death if applicable.

9.5.2 Data Collection

Addition:
Of Arterial pH to-

Baseline Measurement ***and*** *Measurements Following Third Treatment Administration*

Measurements 1 year after the diagnostic procedure

- Therapies received since the diagnostic procedure
- Date of surgery (if any)
- Vital status and date of death, if applicable

9.5.5 Efficacy Variables

Secondary Endpoints-Addition:

4) Change in the ratio of PAPm to SAPm by treatment

5) Survival at 1 year by response

10.4.2 Serious Adverse Events

Changed From:

Any serious adverse event must be reported to INO Therapeutics within 24 hours by telephone to:

Catherine Evans, Regulatory Affairs Associate

Phone: (908) 238-6655

Fax: (908) 238-6635

Dr. James S. Baldassarre

Phone: (908) 238-6363 Cell: (908) 500-8111

Changed To:

All serious adverse events occurring during the study, and within 12 hours of the discontinuation of treatment gas, or hospital discharge whichever comes first, must be reported within 24 hours to INO Therapeutics by fax/telephone to:

Catherine Evans

INO Therapeutics Regulatory Affairs Associate

Phone: + 001 908 238-6655

Fax: +001 908 238-6635

If you have any specific questions regarding an adverse event being classified as serious, you may contact the Medical Monitor for this study:

Dr. James S. Baldassarre

INO Therapeutics Senior Director Research & Development

Phone: +001 908 238-6363

Cell: +001 908 500-8111

Added to text: *"within 24 hours by completing an SAE packet with"*

Delete page 40, second to last paragraph:

All patient/subject deaths will be reported independent of the temporal relationship to the patient's/subject's study participation and treatment (i.e. test drug, placebo).

Appendix 2. Analytic Plan

Section D-page 46/47 Addition:

Change in the Ratio of PA Pressure to Systemic Pressure

It is hypothesized that there is a difference in the ratio of PA pressure to systemic pressure between the NO and O_2 group versus the O_2 alone group. The hypotheses are formerly expressed as:

H_o: There is no difference in the ratio of PAPm to SAPm between the NO and O_2 group versus the O_2 alone group.
The alternative hypothesis is:
H_a: A difference exists in the ratio of PAPm to SAPm between the NO and O_2 group versus the O_2 alone group.

The difference in the ratios for each treatment group will be analyzed using an ANOVA model. The list of independent variables includes, but is not limited to, treatment, subject (nested within treatment sequence) and treatment sequence. Differences in treatment will be assessed with the type I (α) error of 0.05 for statistical significance (2-tailed).

Survival at 1 Year Following the Diagnostic Procedure

It is hypothesized that there is a difference in rates of survival at 1 year of those who met response criteria as outlined in section C of this analytic plan. The hypotheses are formerly expressed as:

H_o: There is no difference in the survival rate of patients with a positive response in PAPm or PVRI between the NO and O_2 group versus the O_2 alone group.
The alternative hypothesis is:
H_a: A difference exists in the survival rate of patients with a positive response in PAPm or PVRI between the NO and O_2 group versus the O_2 alone group.

The difference between the two treatment groups will be tested using the Fisher's Exact Test. This test will be conducted with the type I (α) error of 0.05 for statistical significance (2-tailed). In addition, a Kaplan-Meier plots will be generated for time to death for each treatment group.

APPENDIX 4. LISTING OF AMENDMENT II CHANGES

AMENDMENT II CHANGES:

Cover Page, Version

Changed From:

"Amendment I"

Changed To:

"Amendment II"

Cover Page, Document Date

Changed From:

[redacted]

Changed To:

[redacted]

Cover Page, Duration

Changed From:

"1 ½ years"

Changed To:

"2 years"

Cover Page, Study Contact

Addition:

Sandra Cottrell
VP Global Regulatory Affairs

Synopsis

Investigators

Addition:
et al. TBD

Study Centers

Addition:
et al. TBD

Study Period

Anticipated Completion:

Changed From:

[redacted]

Changed To:

[redacted]

Anticipated duration of trial

Changed From:

1½ years

Changed To:

2 years

Criteria for Evaluation

Secondary Endpoints:

Changed From:

5) Survival at 1 year by response

Changed To:

5) Survival at 1 year and 3 years by response

6.1 Investigators
Changed From:
Approximately 8 sites will participate in the trial with an expected total enrollment of a minimum of 150 patients (approximately 20 patients per site). Enrollment will proceed until at least 25 patients per entry diagnosis are enrolled.

Changed To:
Approximately 18 sites will participate in the trial with an expected total enrollment of a minimum of 150 patients (approximately 9 patients per site).

9.3.2Exlusion Criteria

Addition:

5) Baseline PCWP > 20 mmHg

9.4.2 Identity of Investigational Product

Changed From:
Nitric oxide for inhalation will be supplied in size "88", aluminum cylinders at a concentration of 800 ppm, balance nitrogen (99.92% grade 5 nitrogen, 0.08% pharmaceutical grade nitric oxide).

Changed To:

Nitric oxide for inhalation will be supplied in size "88" US or "10L" EU, aluminum cylinders at a concentration of 800 ppm, balance nitrogen (99.92% grade 5 nitrogen, 0.08% pharmaceutical grade nitric oxide).

9.5 Table 1

Addition to table:

pH- following third treatment administration

Addition to Footnote:

3 year follow up

9.5.2 Data Collection

Changed From:

Measurements 1 year after the diagnostic procedure

Changed To:

Measurements 1 year and 3 years after the diagnostic procedure

9.5.5 Efficacy Variables

Secondary Endpoints

Changed From:

Survival at 1 year by response

Changed To:

Survival at 1 year and 3 years, by response

9.7.1 Sample Size Determination

Changed From:

Using the assumptions listed above, the minimum number of patients required per entry diagnosis is 25. Enrollment will proceed until at least 25 patients per entry diagnosis are enrolled and there are at least 150 patients in the trial.

Changed To:

Enrollment will proceed until at least 150 patients have been enrolled in the trial.

Throughout document:

Changed From:

INO Therapeutics, Inc.

Changed To:

INO Therapeutics, LLC

Appendix 2. Analytic Plan -D. Secondary Efficacy Analysis

Changed From:

Survival at 1 Year Following the Diagnostic Procedure

It is hypothesized that there is a difference in rates of survival at 1year of those who met response criteria as outlined in section C of this analytic plan.

Survival at 1 and 3 Years Following the Diagnostic Procedure

It is hypothesized that there is a difference in rates of survival at 1 and 3 years of those who met response criteria as outlined in section C of this analytic plan.

Appendix 3. Amendment I Changes

Section 9.1

Changed From:

Page 14

Changed To:

Page 19

Appendix 2. Analytic Plan Section D

Changed From:

Page 42/43

Changed To:

Page 46/47

Secondary Endpoints:

Point #5 corrected from #6.

INVESTIGATOR AGREEMENT

Protocol INOT22
Version: Amendment II

I have read the protocol, "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", Protocol INOT22 (version 1), and agree to conduct the study as outlined therein. I will make a reasonable effort to conduct the study in a timely and efficient manner and will ensure that all participating staff members are adequately trained to carry out the tasks for which they have been assigned.

I will submit this protocol and all other pertinent information to my IRB/IEC for approval.

_____ _____
Principal Investigator's Signature Date

_____
Name of investigator (printed)

APPENDIX 4

6 Route 173, Clinton, NJ 08809
Tel (908) 238-6600 Fax (908) 238-6633
http://www.inotherapeutics.com

[redacted]

Center for Drug Evaluation and Research
Office for Drug Evaluation I
Division of Cardio-Renal Drug Products
(HFD-110)
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

IND 63,096
INOmax® (nitric oxide) for inhalation

Serial No.: 091

Protocol Amendment
Change in Protocol
New Investigator: Updated Investigator Information

Dear Sir or Madam:

Reference is made to Investigational New Drug Application 63,096 for the treatment of cardiopulmonary disease and sickle cell disease. At this time we wish to provide amendments to protocols INOT22 and INOT43. Also, we wish to provide new investigator information and an amendment to protocol INOT41 and new investigator information for INOT36.

Protocol INOT22
Comparison of Supplemental Oxygen and Nitric Oxide for Inhalation Plus Oxygenation in the Evaluation of the Reactivity of the Pulmonary Vasculature During Acute Pulmonary Vasodilator Testing. (Originally submitted [redacted] Serial No. 071 and amended [redacted] Serial No. 083)

Below is a list of major changes incorporated into protocol INOT22, Amendment 2.

- Anticipated duration of trial changed from 1 ½ to 2 years.
- Revised investigator sites information from approximately 8 sites with approximately 20 patients per site to approximately 18 sites with approximately 9 patients per site.
- Revised exclusion criteria to add Baseline PCWP> 20 mmHg.
- Revised data collection from 1 year after the diagnostic procedure to 1 year and 3 years after the diagnostic procedure.
- Revised sample size determination from "the minimum number of patients required per entry diagnosis is 25. Enrollment will proceed until at least 25 patients per entry

diagnosis are enrolled and there are at least 150 patients in the trial" to "Enrollment will proceed until at least 150 patients have been enrolled in the trial."

- Appendix 2. Analytic Plan –D. Secondary Efficacy Analysis changed from 1 year to 1 and 3 years.

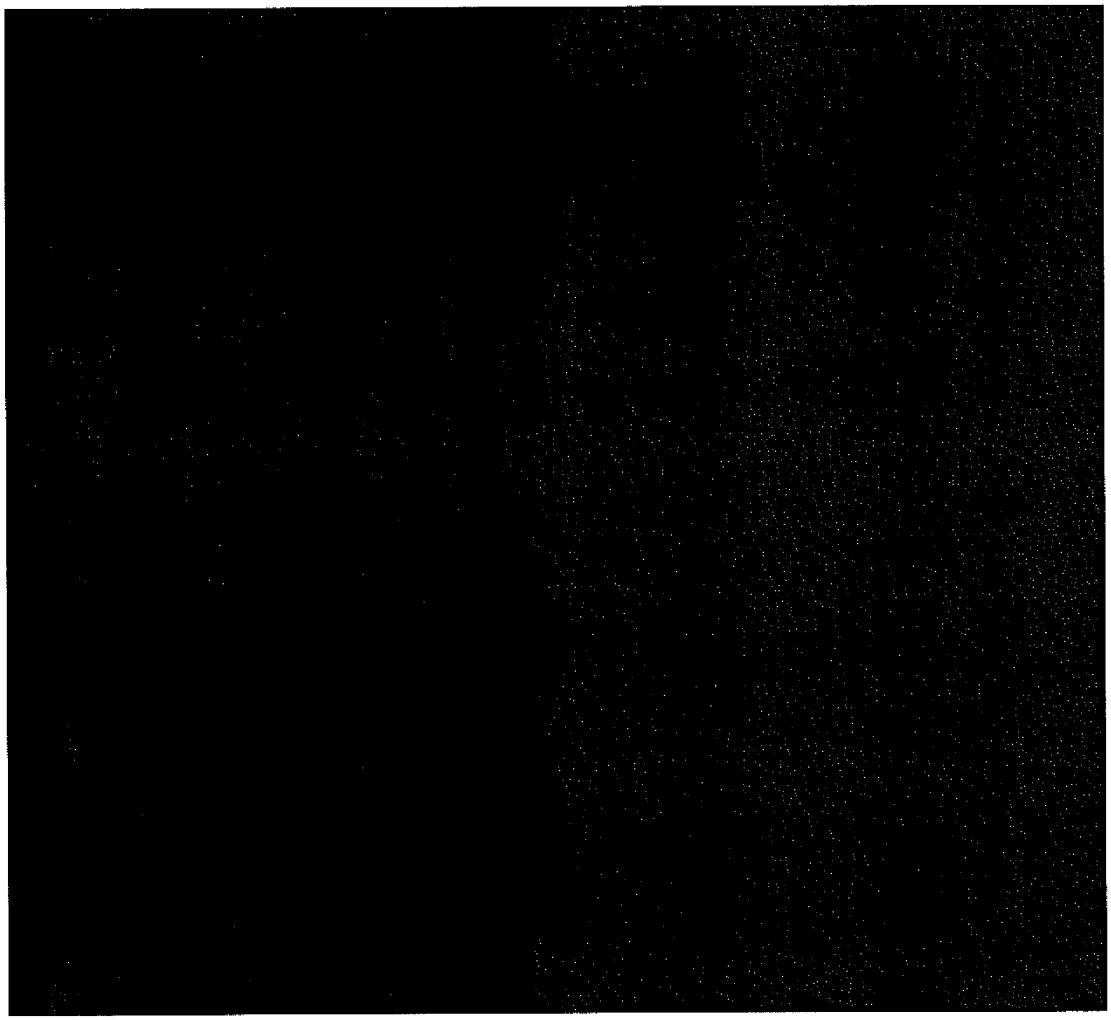
For ease of review, a detailed list of all revisions to this amended protocol is included in appendix 4 of the appended protocol.

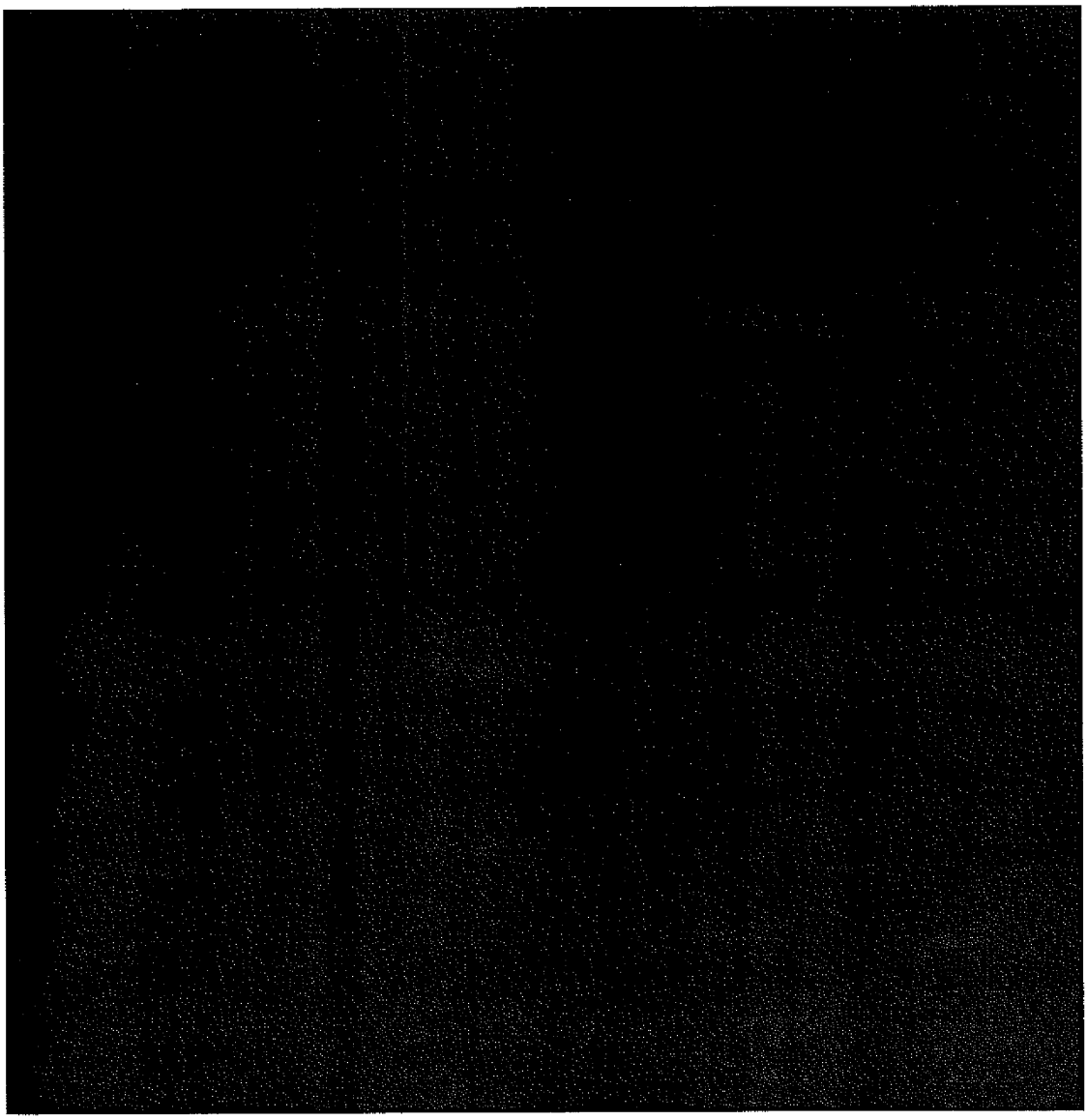
Prior to enrollment of subjects under Amendment 2, further revisions were made to the protocol resulting in Amendment 3.

Below is a list of major changes incorporated into protocol INOT22, Amendment 3.

- Revised sample size information from 150 patients to 100 patients.

For ease of review, a detailed list of all revisions to this amended protocol is included in appendix 5 of the appended protocol.





Should you have any questions and/or comments, please contact me directly at 908-238-6337.

Sincerely,

INO Therapeutics,

Mary Ellen Zamstein

Mary Ellen Zamstein
Director, Regulatory Affairs

F: Regulatory IND 63,096 Protocol Amendments [redacted] FDA letter.doc

APPENDIX 5

[redacted]

From: Debra A. Rimar
Sent: [redacted]
To: James Baldassarre
Subject: FW: INOT22 - latest draft CSR (v.0.3)

Sorry.

Debra Rimar
INO Therapeutics/IKARIA
6 Route 173
Clinton, NJ 08809
debra.rimar@ikaria.com
908.238.6322

From: James Baldassarre
Sent: [redacted]
To: Debra A. Rimar
Subject: RE: INOT22 - latest draft CSR (v.0.3)

There's no attachment.

jim

From: Debra A. Rimar
Sent: [redacted]
To: James Baldassarre
Subject: INOT22 - latest draft CSR (v.0.3)
Importance: High

Jim:

Latest version w/inclusion of two recent tables + new pvri Figure 5 + various minor changes.

See highlighted areas needing possible attention.

Jodee taking Safety section.

Make changes directly in the doct. and return and I will merge into master.

Debra Rimar
INO Therapeutics/IKARIA
6 Route 173

Clinton, NJ 08809
debra.rimar@ikaria.com
908.238.6322

NITRIC OXIDE FOR INHALATION, INOmax®

INOT22

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

Indication studied:	*Diagnostic use*
Developmental phase of study:	*PHASE 3*
First patient enrolled:	*<<Date>>*
Last patient completed:	*<<Date>>*
Release date of report:	*<<Date>>*

Company/Sponsor signatory: *<<Name>>*
<<Telephone Number>>
<<Fax Number>>

This trial was conducted in accordance with the ethical principles of Good Clinical Practice (GCP), according to the International Conference on Harmonisation (ICH) Harmonized Tripartite Guideline.

Sponsor's Responsible Medical Officer <<Signature, Date>>

3. TABLE OF CONTENTS FOR THE INDIVIDUAL CLINICAL STUDY REPORT

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and specialist terms are used in this study report.

Table 1: Abbreviations and Specialist Terms

Abbreviation or specialist term	Explanation
AE	Adverse event
APVT	Acute pulmonary vasodilator testing
CFR	Code of federal regulations
CHD	Congenital heart disease
CI	Cardiac index
CO	Cardiac output
CRA	Clinical research associate
CRF	Case report form
CVPm	Mean central venous pressure
DAP	Diastolic arterial blood pressure
FDA	Food and Drug Administration
GCP	Good Clinical Practice
Hgb	Hemoglobin
HR	Heart rate
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IPAH	Idiopathic pulmonary hypertension
IRB	Institutional Review Board
MAP	Mean arterial pressure
mm Hg	Millimeters of mercury
n	Total number of patients (sample size)
NO	Nitric oxide
NO_2	Nitrogen dioxide
O_2	Oxygen
PAP	Pulmonary arterial pressure

Abbreviation or specialist term	Explanation
PAPm	Mean pulmonary arterial pressure
PAPs	Systolic pulmonary arterial pressure
PAWPm	Mean pulmonary artery wedge pressure
PCWP	Pulmonary capillary wedge pressure
PDE5	Phosphodiesterase type 5
PH	Pulmonary hypertension
ppm	Parts per million by volume (40 pm = 0.004% of the inhaled gas)
PVR	Pulmonary vascular resistance
PVRI	Pulmonary vascular resistance index
SAE	Serious adverse event
SAP	Systolic arterial blood pressure
SAPm	Mean systolic arterial blood pressure

5. ETHICS

5.1. Independent Ethics Committee (IEC) or Institutional Review Board (IRB)

The protocols and local Informed Consent Forms were reviewed and approved by each of the participating institution's IRB/IEC prior to the initiation of patient accrual. The IRB/IEC was notified of all protocol amendments. In addition, progress reports were submitted to the IRB/IEC by the investigator as indicated by the IRB/IEC's guidelines. Each IRB/IEC met the Food and Drug Administration's (FDA) and/or International Conference on Harmonization (ICH) requirements for composition, documentation, and operational procedures. A list of all IECs and IRBs is provided in Appendix 16.1.3 along with the name of the committee chair.

5.2. Ethical Conduct of the Study

This trial was designed and monitored in accordance with INO Therapeutics LLC procedures, which comply with the ethical principles of Good Clinical Practices (GCP) as required by the major regulatory authorities, and in accordance with the Declaration of Helsinki.

5.3. Patient Information and Consent

All patients (or legally authorized representative) provided informed written consent after having had adequate time to consider their participation in the study. Consent was obtained prior to any protocol-related procedures that were not part of the patient's normal care. Written documentation of consent was recorded on a signature page and the patient or their legal representative received a copy of the consent form according to ICH GCP guidelines. A sample of the consent form is provided in Appendix 16.1.3.

6. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

A total of 19 sites participated in the trial with a total enrollment of 136 patients. A listing of principal investigators at each study site and their institutional affiliations is provided in Appendix 16.1.4. Signatures of principal investigators are provided in Appendix 16.1.5.

The study was initiated by INO Therapeutics LLC and a Steering Committee was established to review the contents of the protocol and subsequent amendments, monitor the progress of the trial, and provide recommendations to the sponsors on changes in the procedures and conduct of the trial. Steering Committee members included:

- David Wessel, MD, Boston Children's Hospital, Boston, MA, USA.
- Robyn Barst, MD, Columbia Presbyterian Hospital, New York, NY, USA.
- Duncan Macrae, MD, Royal Brompton Hospital, London, UK.

Due to the short duration of the study, the fact that the treatment assignments were not blinded and the fact that the study endpoints were not serious irreversible events, no Data Safety Monitoring Board was established and no interim analysis of efficacy was carried out. To ensure the well-being of patients enrolled in the trial, safety was monitored on an ongoing basis. All adverse events (AEs) and serious AEs (SAEs) were reviewed by the Steering Committee on a regular basis and reported to the appropriate health authorities and IRBs/IECs as per ICH GCP and as required by local regulations.

7. INTRODUCTION

Pulmonary hypertension (PH) is a condition characterized by elevated pulmonary artery pressures. Pulmonary hypertension may be idiopathic (i.e., without an identified cause) or secondary to other disease processes (e.g., intrinsic heart or lung disease, collagen-vascular disease, toxins or infections).[1,2] In either case, it is associated with changes in the pulmonary vascular bed such as vasoconstriction, vascular-wall remodeling, and thrombosis *in situ* resulting in increased vascular resistance.[2] Abnormal production of vasorelaxants and vasoconstrictors by the pulmonary endothelium may also play a role. Endothelium-derived metabolite imbalances of the vasorelaxant prostacyclin and vasoconstrictor thromboxane have been linked to PH, as have impaired synthesis of the vasorelaxant nitric oxide (NO) and enhanced production of vasoconstrictor endothelin.[2-5] Conventional medical treatments consisting of vasodilators, inotropes, anticoagulants, diuretics or oxygen (O_2) are aimed at decreasing mean pulmonary arterial pressure (PAPm) and pulmonary vascular resistance (PVR). In patients with primary PH and symptomatic right ventricular failure, the median survival time is less than 3 years, and surgical intervention such as heart or heart/lung transplantation may have to be considered.[2,6]

For patients with right ventricular failure and lung disorders, the prognosis and course of treatment are determined by acute pulmonary vasodilation testing (APVT). A reduction in PAPm and PVR with acute vasodilator treatment may be used to predict therapeutic efficacy of long-term vasodilator medication. APVT is also used to evaluate patients being considered for heart or heart/lung transplantation; elevated pulmonary artery pressures and PVR place a strain on the right ventricle, leading to an increased risk of perioperative morbidity and mortality due to right heart failure post-heart transplant.[7-10]

Administration of 100% supplemental O_2 has been a standard in APVT, especially in pediatric patients. However, some patients with reactive pulmonary vasculature fail to respond to acute treatment with 100% supplemental O_2. Nitric oxide has been shown to be selective for the pulmonary versus the systemic vasculature, and it does not increase pulmonary shunting.[11] It has been shown that combination testing with inhaled NO and O_2 provides additional pulmonary vasodilation in patients with a reactive vascular bed, and NO plus O_2 is more effective than O_2 alone when used as a pulmonary vasodilator.[10,11]

INOmax® (Nitric oxide for inhalation) is approved by the FDA for use in term newborns with PH and hypoxic respiratory failure in conjunction with mechanical ventilation and other supportive measures to allow more blood to circulate in the lung, which helps to increase blood O_2 levels.[12] Nitric oxide, the endothelial-derived relaxing factor, is a major physiologic regulator of endothelial smooth muscle tone. In published studies, NO for inhalation has been shown to reduce pulmonary artery pressures in patients with adult respiratory distress syndrome, chronic obstructive lung disease, PH, and congenital heart disease (CHD).[7,8,10,13] Studies in primary and secondary forms of PH have shown that short-term NO for inhalation can selectively reduce both PAPm and PVR with minimal side effects.[7,10] Nitric oxide for inhalation has a short half-life, as it quickly binds to hemoglobin (Hgb) within the pulmonary capillary lumen to form methemoglobin,

rendering it inactive, and systemic vasodilation effects with NO are minimal. Potential risks of NO are rebound PH, increased nitrogen dioxide (NO_2, a lung irritant), and methemoglobinemia. However, due to the short duration of NO delivery in this study, it is unlikely these events would occur.

This study tests the hypothesis that a combination of inhaled NO and O_2 is more sensitive than 100% supplemental O_2 alone in detecting pulmonary vasoreactivity in patients with PH.

This report is intended to report only the primary endpoint and other short-term endpoints. The results of 1- and 3-year follow-up will be reported in subsequent reports, as data becomes available.

8. STUDY OBJECTIVES

The primary objective of the trial was to compare the number of patients with reversible PH (vasoreactivity) due to NO for inhalation and O_2 as compared to 100% O_2. The criteria for response were:

- Patients with idiopathic pulmonary arterial hypertension (IPAH) or patients with CHD who did not have an unrestricted shunt at the level of the ventricle or ductus arteriosus: a decrease in PAPm ≥ 20% and no decrease in cardiac index (CI) (within 5%).
- Patients with cardiomyopathy or patients with CHD who had an unrestricted shunt at the level of the ventricle or ductus arteriosus: a decrease in PAPm ≥ 20% and no decrease in CI (within 5%) or a decrease in PVR index (PVRI) ≥ 25% and no decrease in CI (within 5%).

Additional study objectives were to compare the incidence and types of drug-related AEs and SAEs, as well as the number of patients with reversible PH due to NO for inhalation alone compared to 100% O_2 and to O_2 with NO for inhalation.

9. INVESTIGATIONAL PLAN

9.1. Overall Study Design and Plan: Description

This trial followed an open, prospective, multicenter, randomized controlled design and compared the utility and side effects of O_2, NO, and the combination of NO and O_2 in determining pulmonary reactivity. Each patient was screened for enrollment and fulfilled all entry criteria described in Section 9.3. Upon obtaining informed consent approved by the institution's IRB/IEC, patients were randomly assigned, using a randomization table, to receive either NO for inhalation at 80 parts per million (ppm) or 100% O_2 as their initial dose. Patients were either under general anesthesia or awake sedation. Once the study drug delivery equipment was prepared, baseline data were collected. Using a calibrated INOvent®, either NO for inhalation at 80 ppm or 100% O_2 was continuously administered to the patient for 10 minutes followed by data collection. The second dose was the same as the first dose with the addition of either 80 ppm NO for patients receiving O_2, or 100% O_2 for patients receiving NO. This dose of 80 ppm NO and 100% O_2 was delivered for 10 minutes followed by data collection. There was a 10 minute washout period following this administration. Baseline data were again collected followed by a 10 minute administration of either 80 ppm NO or 100% O_2. The study drug delivered for this third administration was not randomly assigned for the initial study drug administration.

For each patient, NO_2 levels were monitored throughout the treatment period. Treatment with study gas was discontinued if NO_2 levels exceeded 3 ppm. Treatment could also be discontinued at the discretion of the attending physician or following the occurrence of an adverse response to study drug. All AEs were recorded while on study gas. Serious AEs were recorded during the treatment period through Day 1 or discharge from the hospital, whichever came first. Qualification and reporting of all SAEs was carried out as per the Code of Federal Regulations (CFR) and ICH guidelines.

Following the acute diagnostic procedure, a brief follow-up contact was to be made for each patient to determine vital status 1 and 3 years after the study procedure.

9.2. Discussion of the Study Design, Including the Choice of Control Groups

This was an open, randomized, prospective, multicenter, controlled trial designed to demonstrate which diagnostic treatment was most capable of identifying patients with a reactive pulmonary vascular bed. Each patient served as his or her own control and received all three treatment regimens: 80 ppm NO for inhalation, 80 ppm NO and 100% O_2, and the comparison treatment, 100% O_2. Due to the short half-life of NO, a 10 minute washout period following the NO for inhalation and 100% O_2 treatment allowed sufficient time for elimination of the drug effect before administration of the comparison treatment. Only a single study phase without O_2 was included in this trial. This approach

was taken because an additional treatment period without O_2 would have been potentially unsafe for the unstable patients included in this study.

9.3. Selection of Study Population

The patients enrolled in this study had IPAH, CHD (with or without intravascular shunt) with PH, and cardiomyopathies. Patients were stratified based on entry diagnosis and included those who were awake or under general anesthesia. However, after the first 45 patients were enrolled, the protocol was amended such that patients with PCWP > 20 mm Hg were excluded. This was done at the suggestion of the Steering Committee due to the potential risk in that subgroup. The total sample size was reduced from 150 to 100 patients.

9.3.1. Inclusion Criteria

For inclusion into the trial, patients were required to fulfill all of the following criteria:

- Male or female 4 weeks to 18 years of age (inclusive)

  Idiopathic Pulmonary Arterial Hypertension (PAPm >25 mm Hg at rest, pulmonary capillary wedge pressure [PCWP] ≤ 15 mm Hg, and PVRI > 3W u·m^2, or diagnosed clinically with no previous catheterization)
- Congenital heart disease with PH repaired and unrepaired with PAPm > 25 mm Hg at rest, PVRI >3 Wu·m^2, or diagnosed clinically with no previous catheterization
- Scheduled to undergo right heart catheterization to assess pulmonary vasoreactivity by acute pulmonary vasodilation testing
- Signed IRB/IEC approved consent (an assent if applicable)

9.3.2. Exclusion Criteria

Any of the following was regarded as a criterion for exclusion from the trial:

- Focal pulmonary infiltrates on chest radiograph
- PWCP >20 mm Hg
- Diagnosed with severe obstructive or restrictive pulmonary disease that was significantly contributing to the patient's PH
- Received treatment with NO for inhalation within 30 days prior to study initiation, were on other investigational medications, nitroglycerin, sodium nitroprusside, sildenafil, other phosphodiesterase type 5 (PDE5) inhibitors, or prostacyclin
- Were pregnant (positive urine pregnancy test)

9.3.3. Removal of Patients from Therapy or Assessment

Patients were removed from the trial if any of the following circumstances occurred:

- Study gas was discontinued if NO_2 levels exceeded 3 ppm
- Treatment could also be discontinued if the patient or legal representative withdrew consent or if the investigator deemed it in the best medical interest of the patient

9.4. Treatments

9.4.1. Treatments Administered

After obtaining a signed informed consent form, each patient received either NO for inhalation administered using an INOvent® delivery system, or 100% O_2. The INOvent® is designed to add NO at preset levels to a ventilator circuit so that inspired NO concentrations remain unchanged despite changes in ventilation modes.

Patients who were under general anesthesia were intubated and received NO for inhalation, 100% O_2, or a combination of NO and O_2. NO was administered using an INOvent® delivery system through a t-connector downstream of the inspiratory limb of a mechanical ventilator. Patients who were under awake sedation (mild sedation) received NO for inhalation, 100% O_2, or a combination of NO and O_2. The NO was administered using an INOvent® delivery system through a properly fitted, sealed facemask.

Each patient was randomized as to which study drug (80 ppm NO or 100% O_2) they received as the initial dose. The second dose administration was 80 ppm NO for inhalation with 100% O_2 (set - approximate O_2 delivery 90%) and the third dose administration was whichever study drug was not initially administered (NO or 100% O_2). There was a 10 minute washout period between the second and third dose administrations.

9.4.2. Identity of Investigational Products

The active drug, NO for inhalation, was manufactured by INO Therapeutics LLC. Nitric oxide for inhalation was supplied in size "88" US or "10 L" EU aluminum cylinders at a concentration of 800 ppm, balance nitrogen (99.92% grade 5 nitrogen, 0.08% pharmaceutical grade NO). The cylinders were stored in a controlled, limited access area at standard room temperature. Cylinder labels distinguished among sites, but were not pre-assigned patient numbers. The O_2 used in this study was provided by each hospital.

9.4.3. Method of Assigning Patients to Treatment Groups

Randomization of the initial study treatment administered was block randomization by site. Only the first treatment assignment was randomized. The randomization codes were provided to sites in individual envelopes per patient. Patients served as their own controls and received all three treatments.

9.4.4. Selection of Doses in the Study

While varying doses of NO for inhalation have been shown to be safe and effective in decreasing PAPm and PVRI, the use of 80 ppm may elicit a response in a small percentage of nonresponders to lower doses (Wessel D, personal communication, [redacted]). Therefore, 80 ppm of NO for inhalation was used in an effort to capture data from the maximum number of potential responders. Previous studies with NO for inhalation have shown no significant increase in the levels of methemoglobin after very short exposures, even at the dose of 80 ppm.[10,13]

9.4.5. Selection and Timing of Dose for Each Patient

Once informed consent was obtained, the delivery equipment was set up with the appropriate study drug cylinders. Doses of 80 ppm NO for inhalation, 100% supplemental O_2, and 80 ppm NO for inhalation with 100% O_2 (set-approximate O_2 delivery 90%) were administered for at least 10 minutes. The order of the initial treatment was randomized. The second dose administered was always 80 ppm NO for inhalation with 100% O_2 followed by a 10 minute washout period. The third dose was the treatment that was not randomly assigned for the initial study drug administration.

9.4.6. Blinding

Treatment was not blinded. Prior to initial baseline measurements, a cardiac catheter was placed and the drug delivery equipment prepared. The lack of a placebo and the nature of the data being collected (e.g., hemodynamic variables) were expected to be sufficiently objective to eliminate investigator bias.

9.4.7. Prior and Concomitant Therapy

Patients who had received treatment with NO for inhalation within 30 days prior to study initiation, other investigational medications, nitroglycerin, sodium nitroprusside, sildenafil or other PDE5 inhibitors, or prostacyclin were excluded from this trial.

Ketamine was not to be used as part of the anesthetic regimen.

Concomitant medications were recorded on the case report form (CRF).

9.4.8. Treatment Compliance

It was the principal investigator's responsibility to ensure that the treatment, as detailed in the approved protocol, was administered to each enrolled patient. Study drug was administered to patients under the investigator's (or responsible sub-investigator's) direct supervision. All drugs used in the study were accounted for and documented in a usage log provided by the sponsor.

9.4.9. Ventilator Weaning and Extubation Strategy

Following the third treatment administration, study patients under general anesthesia were weaned from the mechanical ventilator and extubated according to standard medical care and hospital specific protocol. Study patients under awake sedation had treatments

discontinued and the facemask removed according to standard medical care and hospital specific protocol.

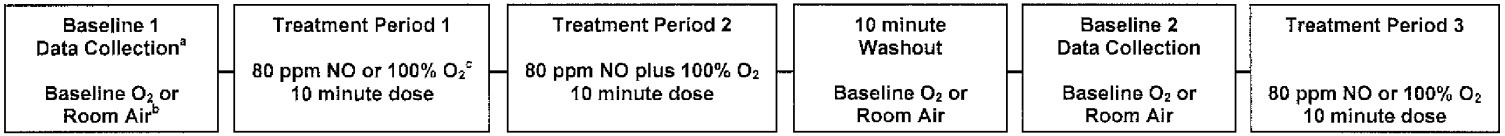
9.5. Efficacy and Safety Variables

9.5.1. Efficacy and Safety Measurements Assessed and Flow Chart

The schedule of assessments is shown in Figure 1 and Table 2. All study procedures were carried out on a single day.

Figure 1: Study Design and Schedule Of Assessments

Data Collection and Treatment



[a] Data collection included hemodynamic measurements and cardiac output (CO)
[b] Baseline measurements were made with room air whenever possible
[c] Patients were randomized as to which treatment would be received first
Follow-up assessments at 1 and 3 years will consist of a brief telephone contact to determine vital status

Table 2: Study Design and Schedule Of Assessments

	Screening	**Baseline** Room air or baseline O_2	**Treatment 1** 80 ppm NO or 100% O_2	**Treatment 2** 80 ppm NO and 100% O_2	**Washout Period**	**Baseline 2**	**Treatment 3** 80 ppm NO or 100% O_2
Informed Consent	X						
Demography		X					
Hgb		X					
Hemodynamic Measurements[a]		X	X	X		X	X
Safety							
AEs[b]			X	X	X	X	X
SAEs[c]			X	X	X	X	X
O_2 consumption		X					
Arterial pH		X					X
Follow-up visit[d]							

[a] Hemodynamic measurements included heart rate (HR), systolic arterial blood pressure (SAP), diastolic arterial blood pressure (DAP), mean arterial pressure (MAP), mean central venous pressure (CVPm), systolic pulmonary arterial pressure (PAPs), diastolic pulmonary arterial pressure (PAPd), PAPm, mean pulmonary artery wedge pressure (PAWPm), and CO.

[b] Adverse events were collected until the patient was discontinued from study gas.

[c] Serious AEs were collected through 12 hours after discontinuation of study gas or discharge, whichever came first. Follow-up assessment at 1 year and 3 years will consist of a telephone call to assess medical therapies or surgical procedures pertaining to pulmonary/cardiac disease, and vital status/date of death if applicable.

[d] Follow-up assessment at 1 and 3 years will consist of a telephone call to assess medical therapies or surgical procedures pertaining to pulmonary/cardiac disease, and vital status/date of death if applicable.

- Baseline measurements included:
  - Compliance with inclusion/exclusion criteria
  - Demographic information and diagnosis (underlying disease)
  - Concomitant medications
  - Hemoglobin (may have been recorded within 1 week of baseline)
  - Hemodynamic parameters: HR, SAP, DAP, MAP, CVPm, PAPs, PAPd, PAPm, PAWPm, and CO (determined by either the Fick or Thermal Dilution method; the method used was recorded in the CRF)
  - Arterial pH
- Measurements following first treatment administration:
  - Hemodynamic parameters: HR, SAP, DAP, MAP, CVPm, PAPs, PAPd, PAPm, PAWPm, and CO
  - Adverse events (until the patient is discontinued from study gas) and SAEs (through study Day 1 or discharge, whichever came first)
- Measurements following second treatment administration:
  - Hemodynamic parameters: HR, SAP, DAP, MAP, CVPm, PAPs, PAPd, PAPm, PAWPm, and CO
- Measurements following third treatment administration:
  - Hemodynamic parameters: HR, SAP, DAP, MAP, CVPm, PAPs, PAPd, PAPm, PAWPm, and CO
  - Arterial pH
- Measurements 1 and 3 years after the diagnostic procedure:
  - Therapies received since the diagnostic procedure
  - Date of surgery (if any)
  - Vital status and date of death, if applicable

9.5.2. Recording of Adverse Events

Each patient was assessed for any new or continuing AEs by the investigator or study coordinator. An AE was defined as any untoward medical occurrence. An AE need not have a causal relationship with treatment and included any event that was not seen at baseline or, if present at baseline, increased in severity. Any AE reported by the caregiver or noted by the investigator or study coordinator was recorded on the AE pages in the CRF. The severity and drug relationship were determined and any management required was also noted. Each AE was followed until resolution or discontinuation of study drug, whichever occurred first. The investigator also reviewed clinical laboratory test results and those qualifying as AEs were recorded in the AE section of the CRF.

9.5.2.1. Relationship of Adverse Events to Study Drug

The investigator was responsible for assessing the causal relationship between AEs and study treatment. Additionally, the investigator was responsible for providing appropriate treatment for the event and for adequately following the event until resolution. The investigator determined the study drug relationship to AEs using the following explanations:

- Not related: the event was clearly related to other factors, such as the patient's clinical state, therapeutic interventions, or concomitant drugs administered.
- Remote: the event was most likely produced by other factors, such as the patient's clinical state, therapeutic interventions, or concomitant drugs administered and did not follow a known response pattern to the study drug.
- Possible: the event followed a reasonable temporal sequence from the time of study drug administration or a known response pattern to the study drug, but could have been produced by other factors, such as the patient's clinical state, therapeutic interventions, or concomitant drugs administered.
- Probable: the event followed a reasonable temporal sequence from the time of study drug administration or a known response pattern to the study drug and could not be reasonably explained by other factors, such as the patient's clinical state, therapeutic interventions, or concomitant drugs administered.
- Highly probable: the event followed a reasonable temporal sequence from the time of study drug administration or a known response pattern to the study drug and could not be reasonably explained by other factors, such as the patient's clinical state, therapeutic interventions, or concomitant drugs administered; and either occurred immediately following study drug administration, improved following stopping the drug, or reappeared upon repeat exposure.

Temporal sequence was defined as an association between the suspect drug and the observed reaction in which the suspect drug was present prior to the reaction or event.

9.5.2.2. Severity of Adverse Events

Severity of an AE was defined from the qualitative assessment of the degree of intensity of the event as determined by the investigator or reported to him or her by the patient. The assessment of severity was made irrespective of drug relationship or seriousness of the AE and was evaluated according to the following categories:

- Mild: awareness of the symptom, but easily tolerated
- Moderate: discomfort enough to interfere with normal activities
- Severe: incapacitating with the inability to perform normal activities

9.5.2.3. Serious Adverse Events

An SAE was defined as any event that resulted in death, was life threatening, resulted in permanent disability or incapacity, required or prolonged inpatient hospitalization, or was a congenital anomaly. Important medical events that, without medical or surgical intervention, would also have resulted in one of the outcomes listed above were also considered as SAEs. All

SAEs occurring during the study and within 12 hours after discontinuation of treatment gas or hospital discharge, whichever came first, were to be reported to INO Therapeutics LLC within 24 hours by fax or telephone.

Patients were monitored carefully until SAEs resolved, reached a clinically stable endpoint, or the etiology was defined. The initial telephone contact was followed within 24 hours by completion of an SAE packet with detailed descriptions of the event and supported as needed with written copies of hospital case reports, autopsy reports, and other documents, as applicable.

All SAEs were reported to the IRB/IEC and appropriate local regulatory agency in writing.

9.5.2.4. Unexpected Adverse Events

An unexpected AE was any event that was not identified in nature, severity, or frequency in the current investigator's brochure.

All unexpected AEs were reported to the IRB/IEC and appropriate local regulatory agency in writing.

9.5.3. Appropriateness of Measurements

Demographic and baseline data were collected and evaluated in an attempt to demonstrate that the treatment groups were well balanced with respect to age, sex, race, and that there were no substantial differences in either population with respect to underlying disease. The measured and calculated values in this study are used in standard clinical practice to assess pulmonary vasoreactivity. Both the PAPm and the PVRI have been shown to be useful parameters in measuring the body's response to vasoactive drug therapy.

9.5.4. Efficacy Variables

9.5.4.1. Primary Efficacy Variable

The primary efficacy variable was the number of patients receiving a combination of NO and O_2 versus the number of patients receiving O_2 alone that met response criteria for a pulmonary vasoreactivity response. The response criteria were as follows:

- Patients with IPAH or patients with CHD who did not have an unrestricted shunt at the level of the ventricle or ductus arteriosus: a decrease in PAPm ≥20% and no decrease in CI (within 5%)
- Patients with cardiomyopathy or CHD who had an unrestricted shunt at the level of the ventricle or ductus arteriosus: a decrease in PAPm ≥20% and no decrease in CI (within 5%) or a decrease in PVRI ≥25% and no decrease in CI (within 5%)

9.5.4.2. Secondary Efficacy Variables

Secondary efficacy variables included:

- The number of patients receiving NO versus the number of patients receiving O_2 that met response criteria, as defined above
- The number of patients receiving a combination of NO and O_2 versus the number of patients receiving NO alone that met response criteria, as defined above

- PVRI, PAPm, and CI readings in room air versus NO alone, O_2 alone, and the combination of NO and O_2
- Change in the ratio of PAPm to MAP by treatment
- Survival at 1 and 3 years by response

9.5.5. Drug Concentration Measurements

The INOvent® gas delivery system measures the flow of gas in the ventilator circuit and a mass flow controller adds NO to the ventilator gas flow to create the desired concentration. The device continuously samples gas from the side port adapter and measures O_2, NO, and NO_2 with electrochemical monitors.

9.5.6. Safety Variables

The following safety variables were assessed throughout the treatment gas administration period:

- Incidence and types of reported SAEs
- Incidence and types of reported drug-related AEs

9.6. Data Quality Assurance

Prior to study initiation, meetings were carried out to prepare investigators and standardize performance at each study center. Data were collected by the study site coordinator and verified at the site by the clinical research associate (CRA). This data was monitored and verified 100% to the medical charts. Data were double key entered into a validated Oracle Clinical database managed by INO Therapeutics LLC. Discrepancies were flagged and the database manager made all decisions regarding flags. The trial staff at the hospital made data corrections as necessary.

INO Therapeutics LLC conducts clinical trials according to procedures that incorporate the ethical principles of GCP. To ensure compliance with these procedures and to assess the adequacy of quality control procedures, INO Therapeutics LLC undertakes a GCP audit program.

Audits are performed by a representative of INO Therapeutics LLC who operates independently of the trial monitors. The audits within a clinical program are aimed at trial documentation, investigator sites, and clinical trial reports.

The audit program, together with INO Therapeutics LLC's internal quality control procedures, provides reassurance that trial conclusions are based on valid procedures for data management and analysis, and that the clinical trial program is carried out in accordance with GCP guidelines.

9.7. Statistical Methods Planned in the Protocol and Determination of Sample Size

9.7.1. Statistical and Analytical Plans

All efficacy and safety analyses were carried out on all patients randomized (an intent-to-treat basis). The intent-to-treat population included all patients randomized regardless of actual receipt of treatment gas, the treatment gas actually received, or the appropriateness of their enrollment.

9.7.2. Analysis of Baseline Characteristics

The distributions of all baseline characteristics (age, sex, race, etc.) were tabulated for all patients in the intent-to-treat population.

9.7.3. Primary Efficacy Analysis

The primary efficacy variable for this trial was the number of patients that met criteria for a pulmonary vasoreactivity response (see Section 9.5.4.1). The difference in the primary efficacy variable between treatment with NO plus O_2 versus O_2 alone was compared with the McNemar Test for Significance of Changes. This test was conducted with a type I (α) error of 0.05 for statistical significance (2-tailed).

9.7.4. Secondary Efficacy Analyses

Analysis of all secondary efficacy variables was conducted with a type I (α) error of 0.05 for statistical significance (2-tailed).

The numbers of patients who met the response criteria for a pulmonary vasoreactivity response during treatment with NO versus O_2 and NO versus NO plus O_2 were compared with the McNemar Test for Significance of Changes. These tests were conducted with a type I (α) error of 0.05 for statistical significance (2-tailed).

Differences in PVR, PAPm, and CO in room air versus each treatment were compared with paired t-tests if the normality assumption was not violated, or the Wilcoxon Signed Ranks test if there was a violation of normality. All tests were conducted with a type I (α) error of 0.05 for statistical significance (2-tailed).

The difference in the ratios of PAPm to MAP for the NO plus O_2 versus O_2 was analyzed using an analysis of variance (ANOVA) model. The list of independent variables included treatment, patient (nested within treatment sequence), and treatment sequence. Differences among treatments were assessed with a type I (α) error of 0.05 for statistical significance (2-tailed).

9.7.5. Adverse Events

Analysis of AEs was performed on the number and types of all AEs, treatment-related AEs, and SAEs reported during each treatment. The incidences of all AEs, treatment-related AEs, and SAEs were stratified by MedDRA terms, MedDRA body system, and patients with each type of

AE were tabulated. Additionally, all AEs, treatment-related AEs, and SAEs were stratified by age, sex and race.

9.7.6. Determination of Sample Size

The following assumptions were made:

- The desired type I (α) error of 0.05 was the threshold for statistical significance (2-tailed).
- The expected percentage of patients who had a reduction in PVR of $\geq$ 20% using 80 ppm NO and 100% O_2 and a reduction in PVR of $\leq$ 20% using 100% O_2 would be 24%.[7]
- The expected percentage of patients who had a reduction in PVR of > 20% using 100% O_2 and a reduction in PVR of < 20% using 80 ppm NO and 100% O_2 would be 0%.[7]
- The desired power (1 - β) for the trial was 80%.

Using the assumptions listed above, the minimum number of patients required per entry diagnosis was 25. Enrollment proceeded until at least 25 patients per entry diagnosis were enrolled and there were at least 100 patients in the trial.

9.7.7. Interim Analyses

No interim analyses were carried out.

9.8. Changes in the Conduct of the Study or Planned Analyses

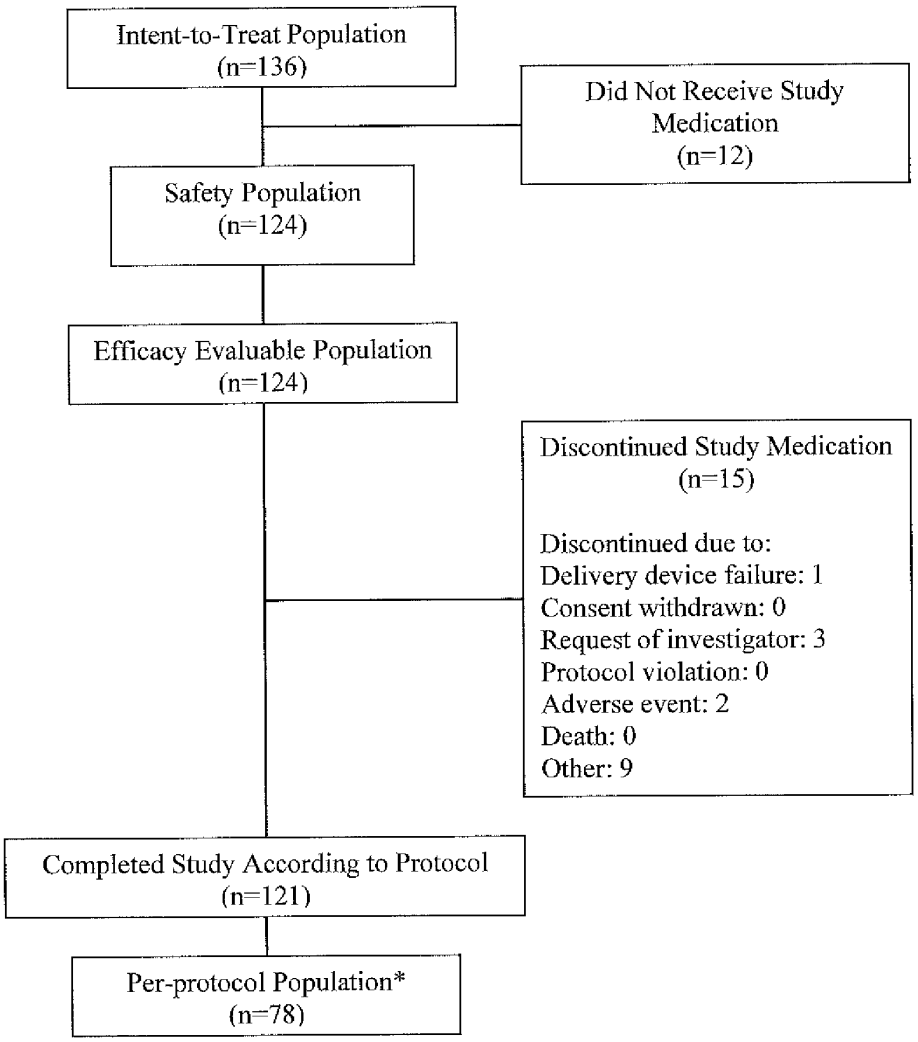
There were no significant changes in the planned conduct of the study or in any analyses.

10. STUDY PATIENTS

10.1. Disposition of Patients

Patient disposition is summarized in Figure 2 and Table 3. The intent-to-treat population included 136 patients and the safety and efficacy-evaluable populations each included 124 patients. Overall, 121 (89.0%) patients completed the study. The per-protocol population consisted of all study completers who had a baseline PVRI > 3. The most common reason for discontinuation was request of the investigator (2.2%) followed by AEs (1.5%).

Figure 2: Patient Disposition



* The per-protocol population had a baseline PVRI > 3. The other 43 patients who completed the study according to the protocol did not have the required PVRI at baseline.

Table 3: Patient Disposition and Reasons For Discontinuation

Analysis Population	Number (%)
ITT	136 (100)
Safety	124 (91.2)
Efficacy Evaluable[a]	124 (91.2)
Per-protocol[b]	78 (57.4)
Completed Study According to Protocol	121 (89.0)
Discontinued Study Medication	15 (11.0)
Primary Reason For Discontinuation	
Delivery Device Failure	1 (0.7)
Consent Withdrawn	0 (0.0)
Request of Investigator	3 (2.2)
Protocol Violation	0 (0.0)
AE	2 (1.5)
Death	0 (0.0)
Other	9 (6.6)

[a] Patients who took study medication
[b] Patients with baseline PVRI > 3
Source: Section 14.1, Table 1, and Appendix 16.2.1

10.2. Protocol Deviations

A total of 123 protocol deviations occurred, none of which required exclusion of patients from the efficacy evaluable population. Deviations from the protocol were categorized as follows:

- Informed Consent (n = 34; most frequently, the use of an outdated Informed Consent Form)
- Inclusion/Exclusion Criteria (n = 6; missed diagnoses of either the underlying cardiovascular condition or pulmonary disease; use of an excluded medication)
- Study Procedures and Examinations (n = 75; most frequently, incorrect timing of measurements; pregnancy test not performed; and PaO_2 not determined)
- Device Use and Maintenance (n = 5; missed monthly calibration of equipment and related)
- SAE Reporting and Documentation (n = 3)

A complete listing of protocol deviations can be found in Appendix 16.2.2.

11. EFFICACY EVALUATION

11.1. Data Sets Analyzed

11.1.1. Study Gas Exposure

The mean times for exposure to study gas were very similar for NO plus O_2 (15.5 minutes), O_2 (15.9 minutes), and NO (15.3 minutes) (Table 4).

Table 4: Study Gas Exposure By Treatment (Intent-to-Treat)

Treatment Duration (minutes)[a]	NO Plus O_2	O_2	NO
N	123	122	123
Mean	15.5	15.9	15.3
SD	5.53	6.54	4.90
Median	14.0	15.0	15.0
Minimum, maximum	5.0, 33.0	7.0, 51.0	8.0, 34.0

[a] Duration (minutes) = (stop time of treatment – start time of treatment) + 1
Source: Section 14.1, Table 2

11.2. Demographic and Other Baseline Characteristics

The demographic and baseline characteristics of the intent-to-treat and per-protocol populations are summarized in Tables 5 and 6. The mean age for the patients in the intent-to-treat population was 5.9 years, 50.0% were male, 59.6% were white, and 40.4% were black. The diagnosis was IPAH in 22.1%, cardiomyopathy in 4.4%, and CHD with PH in 73.5%.

Table 5: Demographics and Baseline Characteristics (Intent-to-Treat)

Characteristic	Intent-to-Treat Population (n=136)
Age (years)	
Mean	5.9
SD	5.58
Median	3.4
Minimum, maximum	0.1, 18.7
≤ 10 (n [%])	98 (72.1)
> 10 (n [%])	38 (27.9)

Table 5: Demographics and Baseline Characteristics (Intent-to-Treat) (Continued)

Characteristic	Intent-to-Treat Population (n=136)
Sex (n [%])	
Male	68 (50.0)
Female	68 (50.0)
Race (n [%])	
White	81 (59.6)
Black	55 (40.4)
Height (cm)	
Mean	101.6
SD	38.02
Median	93.8
Minimum, maximum	50.0, 181.0
Weight (kg)	
Mean	20.0
SD	17.23
Median	14.0
Minimum, maximum	2.7, 70.0
Diagnosis (n [%])	
IPAH	30 (22.1)
Cardiomyopathy	6 (4.4)
CHD With PH	100 (73.5)
Shunt	75 (75.0)
No Shunt	25 (25.0)
Baseline Hgb (g/dL)	
Mean	12.7
SD	2.31
Median	12.5
Minimum, maximum	7.8, 21.0

Table 5: Demographics and Baseline Characteristics (Intent-to-Treat) (Continued)

Characteristic	Intent-to-Treat Population (n=136)
Supplemental O_2 (n [%])	
Yes	30 (22.1)
No	106 (77.9)
Diagnosis Method (n [%])	
Fick	103 (75.7)
Thermodilution	29 (21.3)
Missing	4 (2.9)

Source: Section 14.1, Table 3.1 and Appendix 16.2.4.

The mean age for the patients in the per-protocol population was 7.4 years, 48.7% were males, 65.4% were white and 34.6% were black. The diagnosis was IPAH in 32.1%, cardiomyopathy in 1.3%, and CHD with PH in 66.7%.

Table 6: Demographics and Baseline Characteristics (Per-protocol)

Characteristic	Per-protocol (n=78)
Age (years)	
Mean	7.4
SD	5.80
Median	8.1
Minimum, maximum	0.1, 18.7
≤10 (n [%])	47 (60.3)
>10 (n [%])	31 (39.7)
Sex (n [%])	
Male	38 (48.7)
Female	40 (51.3)
Race (n [%])	
White	51 (65.4)
Black	27 (34.6)
Height (cm)	
Mean	110.9

Characteristic	Per-protocol (n=78)
SD	39.13
Median	115.8

Table 6: Demographics and Baseline Characteristics (Per-protocol) (Continued)

Characteristic	Per-protocol (n=78)
Minimum, maximum	50.0, 181.0
Weight (kg)	
Mean	23.9
SD	18.42
Median	21.5
Minimum, maximum	2.7, 70.0
Diagnosis (n [%])	
IPAH	25 (32.1)
Cardiomyopathy	1 (1.3)
CHD With PH	52 (66.7)
Shunt	34 (65.4)
No Shunt	18 (34.6)
Baseline Hgb (g/dL)	
Mean	13.3
SD	2.46
Median	13.3
Minimum, maximum	7.8, 21.0
Supplemental O_2 (n [%])	
Yes	19 (24.4)
No	59 (75.6)
Diagnosis Method (n [%])	
Fick	55 (70.5)
Thermodilution	23 (29.5)

Source: Section 14.1, Table 3.2 and Appendix 16.2.4

11.2.1. Concomitant Medications

Concomitant medications are summarized in Table 7. The most common concomitant medications were heparin, sevoflurane, fentanyl, propofol, midazolam, nalbuphine, atropine, chloral hydrate, midazolam hydrochloride, vecuronium, paracetamol, cefamandole, and furosemide.

Table 7: Concomitant Medications During The Study Period (Intent-to-Treat)

Medication[a, b] (n [%])	Intent-to-Treat Population (n=136)
Heparin	67 (49.3)
Sevoflurane	47 (34.6)
Fentanyl	44 (32.4)
Propofol	44 (32.4)
Midazolam	41 (30.1)
Nalbuphine	34 (25.0)
Atropine	23 (16.9)
Chloral Hydrate	22 (16.2)
Midazolam Hydrochloride	18 (13.2)
Vecuronium	16 (11.8)
Paracetamol	15 (11.0)
Cefamandole	14 (10.3)
Furosemide	13 (9.6)
Alfentanil Hydrochloride	10 (7.4)
Atracurium	9 (6.6)
Cisatracurium Besilate	9 (6.6)
Ondansetron Hydrochloride	9 (6.6)
Clorazepate Dipotassium	8 (5.9)
Morphine	8 (5.9)
Rocuronium	8 (5.9)
Diclofenac	7 (5.1)
Bosentan	6 (4.4)
Cefazolin	6 (4.4)
Hydroxyzine Hydrochloride	6 (4.4)
Lidocaine	6 (4.4)
Nifedipine	6 (4.4)

Medication[a, b] (n [%])	Intent-to-Treat Population (n=136)
Remifentanil	6 (4.4)
Sodium Bicarbonate	6 (4.4)

[a] A patient taking a medication multiple times is counted only once for that medication.
[b] Medications taken by > 5 patients
Source: Section 14.1, Table 4 and Appendix 16.2.5

11.3. Measurements of Treatment Compliance

Of the 136 patients enrolled into this study, 124 received study medication according to protocol. The time on treatment ranged between 5 to 33 minutes for patients on NO plus O_2, between 7 and 51 minutes for patients on O_2 alone, and between 8 and 34 minutes for patients on NO only.

11.4. Efficacy Results and Tabulations of Individual Patient Data

11.4.1. Analysis of Efficacy

11.4.2. Primary Efficacy Variable

The primary objective was to compare the number of patients with reversible pulmonary hypertension (vasoreactivity) demonstrated by NO for inhalation 80 ppm plus O_2 90% as compared to 100% O_2 alone. Study results for the intent-to-treat population (Table 8) indicated a significantly higher response rate (25.7%) for NO plus O_2 versus O_2 alone (14.7%) ($p = 0.019$). In addition, 17.4% of patients responded only to NO plus O_2 versus 6.4% who only responded to O_2 alone.

Table 8: Pulmonary Vasoreactivity Response By Treatment - NO Plus O_2 Versus O_2 (Intent-to-Treat)

Treatment: NO Plus O_2 (n=109)			
	Nonresponder (n [%])	**Responder[a] (n [%])**	**p-value[b]**
Treatment: O_2			
Nonresponder	74 (67.9)	19 (17.4)	0.019
Responder	7 (6.4)	9 (8.3)	

[a] At least a 20% reduction in PAPm as compared to baseline and no decrease in CI (within 5%) for all patients or at least a 25% reduction in PVRI and no decrease in CI (within 5%) for patients with cardiomyopathy or patients with CHD who have an unrestricted shunt at the level of the ventricle or ductus arteriosus.

[b] p-value from a McNemar test. Only patients with data to determine response at both treatments are included in this analysis.

Source: Section 14.2.1, Table 5.1.1 and Appendix 16.2.6

Baseline pulmonary vascular resistance is a clinically important indicator of disease severity. Because a significant proportion of patients in this study had a baseline PVRI lower than that required for enrollment into the study, the overall disease severity is likely to be somewhat lower than that which had been expected at study inception. For this reason, we decided to include analyses of the 'per-protocol' population. Similar trends were noted for response in the per-protocol population as in the ITT population. There was a higher response rate (22.2%) for NO plus O_2 versus O_2 alone (11.5%). The magnitude of this effect appears to be greater than that seen in the ITT population, but this difference did not achieve statistical significance ($p = 0.071$) due to the smaller sample size (Table 9). In this population, 15.3% of patients responded only to NO plus O_2 versus 4.6% who responded only to O_2.

Table 9: Pulmonary Vasoreactivity Response By Treatment - NO Plus O_2 Versus O_2 (Per-protocol)

Treatment: NO Plus O_2 (n=72)			
	Nonresponder (n [%])	**Responder[a] (n [%])**	**p-value[b]**
Treatment: O_2			
Nonresponder	52 (72.2)	11 (15.3)	0.071
Responder	4 (4.6)	5 (6.9)	

[a] At least a 20% reduction in PAPm as compared to baseline and no decrease in CI (within 5%) for all patients or at least a 25% reduction in PVRI and no decrease in CI (within 5%) for patients with cardiomyopathy or patients with CHD who have an unrestricted shunt at the level of the ventricle or ductus arteriosus.

[b] p-value from a McNemar test. Only patients with data to determine response at both treatments are included in this analysis.

Source: Section 14.2.1, Table 5.1.2 and Appendix 16.2.6

The presence or absence of a significant intracardiac shunt is another important clinical consideration. The majority of patients in this study had an intracardiac shunt. We analyzed the treatment effect in the subset of patients without a shunt. Results for NO plus O_2 versus O_2 alone for patients without shunts were similar to those for the overall population (Table 10). Overall, 22.5% of these patients responded to NO plus O_2 versus 8.2% for O_2 alone (p=0.035).

Table 10: Pulmonary Vasoreactivity Response By Treatment - NO Plus O_2 Versus O_2 - Patients Without Shunts, (Intent-to-Treat)

Treatment: NO Plus O_2 (n=49)			
	Nonresponder (n [%])	**Responder[a] (n [%])**	**p-value[b]**
Treatment: O_2			
Nonresponder	36 (73.5)	9 (18.4)	0.035
Responder	2 (4.1)	2 (4.1)	

[a] At least a 20% reduction in PAPm as compared to baseline and no decrease in CI (within 5%) for all patients or at least a 25% reduction in PVRI and no decrease in CI (within 5%) for patients with cardiomyopathy or patients with CHD who have an unrestricted shunt at the level of the ventricle or ductus arteriosus.

[b] p-value from a McNemar test. Only patients with data to determine response at both treatments are included in this analysis.

Source: Section 14.2.1 Table 5.1.3 and Appendix 16.2.6

Results for NO plus O_2 versus O_2 alone for patients without shunts in the per-protocol population were similar to those for the overall population (Table 11). Overall, 21.9% of these patients responded to NO plus O_2 versus 4.8% for O_2 alone (p=0.020).

Table 11: Pulmonary Vasoreactivity Response By Treatment - NO Plus O_2 Versus O_2 - Patients Without Shunts (Per-protocol)

Treatment: NO Plus O_2 (n=41)			
	Nonresponder (n [%])	**Responder[a] (n [%])**	**p-value[b]**
Treatment: O_2			
Nonresponder	31 (75.6)	8 (19.5)	0.020
Responder	1 (2.4)	1 (2.4)	

[a] At least a 20% reduction in PAPm as compared to baseline and no decrease in CI (within 5%) for all patients or at least a 25% reduction in PVRI and no decrease in CI (within 5%) for patients with cardiomyopathy or patients with CHD who have an unrestricted shunt at the level of the ventricle or ductus arteriosus.

[b] p-value from a McNemar test. Only patients with data to determine response at both treatments are included in this analysis.

Source: Section 14.2.1, Table 5.1.4 and Appendix 16.2.6

11.4.3. Secondary Efficacy Variables

There was no significant difference between responsivity to NO alone versus O_2 alone in the intent-to-treat population (Table 12). The response rate for NO was 23.6% and that for O_2 was 15.1% (p=0.117). For this comparison, 19.8% of patients responded only to NO versus 11.3% for O_2.

Table 12: Pulmonary Vasoreactivity Response By Treatment - NO versus O_2 (Intent-to-Treat)

Treatment: NO (n=106)			
	Nonresponder (n [%])	**Responder[a] (n [%])**	**p-value[b]**
Treatment: O_2			
Nonresponder	69 (65.1)	21 (19.8)	0.117
Responder	12 (11.3)	4 (3.8)	

[a] At least a 20% reduction in PAPm as compared to baseline and no decrease in CI (within 5%) for all patients or at least a 25% reduction in PVRI and no decrease in CI (within 5%) for patients with cardiomyopathy or patients with CHD who have an unrestricted shunt at the level of the ventricle or ductus arteriosus.

[b] p-value from a McNemar test. Only patients with data to determine response at both treatments are included in this analysis.

Source: Section 14.2.2, Table 5.2.1 and Appendix 16.2.6

Overall results for the per-protocol population supported those for the intent-to-treat population. The response rates for NO and O_2 were 15.5% and 12.7%, respectively (p = 0.617). In this population, 12.7% of patients responded only to NO versus 9.9% for O_2.

Results for patients without shunts in the intent-to-treat population indicated that 27.1% responded to NO and 8.4% responded to O_2 (p = 0.020).

Comparison of results for NO alone versus NO plus O_2 in the intent-to-treat population indicated no significant differences in pulmonary vasoreactivity response (Table 13). The response rate for NO was 24.1% and that for NO plus O_2 was 26.9% (p = 0.602). In this comparison, 13.9% of patients responded only to NO versus 16.7% for NO plus O_2.

Table 13: Pulmonary Vasoreactivity Response By Treatment - NO Versus NO Plus O_2 (Intent-to-Treat)

Treatment: NO Plus O_2 (n=108)			
	Nonresponder (n [%])	**Responder[a] (n [%])**	**p-value[b]**
Treatment: NO			
Nonresponder	64 (59.3)	18 (16.7)	0.602
Responder	15 (13.9)	11 (10.2)	

[a] At least a 20% reduction in PAPm as compared to baseline and no decrease in CI (within 5%) for all patients or at least a 25% reduction in PVRI and no decrease in CI (within 5%) for patients with cardiomyopathy or patients with CHD who have an unrestricted shunt at the level of the ventricle or ductus arteriosus.

[b] p-value from a McNemar test. Only patients with data to determine response at both treatments are included in this analysis.

Source: Section 14.2.2, Table 5.3.1 and Appendix 16.2.6

Results for the per-protocol population supported those for the ITT population. The response rate for NO was 16.4% and that for NO plus O_2 was 23.3% ($p = 0.251$). In this population, 9.6% of patients responded only to NO versus 16.4% for NO plus O_2

Results for patients without shunts in the intent-to-treat population indicated that 24.0% responded to NO plus O_2 and 28.0% responded to NO alone ($p = 0.617$).

There was no significant difference in the rate of pulmonary vasoreactivity for patients with or without shunts in either the intent-to-treat or per-protocol populations. In the intent-to-treat population, 45.9% of patients with shunts responded to at least one intervention, versus 46.2% of those without shunts ($p = 1.000$). The respective values for the per-protocol population were 38.7% and 39.5% ($p = 1.000$).

There was no significant difference in the rate of pulmonary vasoreactivity for patients with or without intubation in either the intent-to-treat or per-protocol populations. In the intent-to-treat population, 39.7% of intubated patients responded to at least one intervention versus 52.7% of those who were not intubated ($p = 0.189$). The respective values for the per-protocol population were 33.3% and 43.9% ($p = 0.473$).

Diagnosis significantly influenced the rate of pulmonary vasoreactivity in the intent-to-treat population (Table 14). In the intent-to-treat population, response rates were 42.0%, 48.1%, and 100% for patients with CHD, idiopathic disease, and cardiomyopathy, respectively ($p = 0.034$). The respective values in the per-protocol population were 35.4%, 44.0%, and 100% ($p = 0.366$).

Table 14: Pulmonary Vasoreactivity By Diagnosis (Intent-to-Treat)

	Diagnosis			
	CHD (n [%])	**Idiopathic (n [%])**	**Cardiomyopathy (n [%])**	**p-value[b]**
Response				
Responder[a]	34 (42.0)	13 (48.1)	5 (100.0)	0.034
Nonresponder	47 (58.0)	14 (51.9)	0 (0)	

[a] At least a 20% reduction in PAPm as compared to baseline and no decrease in CI (within 5%) for all patients or at least a 25% reduction in PVRI and no decrease in CI (within 5%) for patients with cardiomyopathy or patients with CHD who have an unrestricted shunt at the level of the ventricle or ductus arteriosus.

[b] p-value from a Fisher Exact test. Only patients with data to determine response at both treatments are included in this analysis.

Source: Section 14.2.2, Table 5.6.1 and Appendix 16.2.6

All treatments significantly decreased PVRI (Figure 3 and Tables 15 and 16). In the intent-to-treat population, the mean changes from baseline with NO plus O_2, O_2 and NO were -2.9, -1.5, and -1.1 $WU \cdot m^2$, respectively (all $p<0.001$ versus baseline). The between-treatment comparisons were also significantly different. The NO plus O_2 was significantly different than both NO and O_2 alone ($p = <0.001$). However, NO alone was not significantly different from O_2 alone ($p = 0.171$). Patients with no shunt provided similar results. A scatter plot of the PVRI change from baseline comparing NO plus O_2 versus O_2 alone is presented in Figure 4.