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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] ¡	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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	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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	First Named Inventor	Baldassarre
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	Attorney Docket Number	26047-0003011

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	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)	☐
	26	Germann et al., "Inhaled nitric oxide therapy in adults: European expert recommendations," Intensive Care Med, 31:1029-1041 (June 2005)	☐
	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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	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)	☐

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 (**Not for submission under 37 CFR 1.99)**	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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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 _____

      ii. ☐ Other _____

   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

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Mail Stop RCE, Commissioner for Patents, P. O. Box 1450, Alexandria, VA 22313-1450 or facsimile transmitted to the U.S. Patent and Trademark Office on the date shown below.

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

23348928.doc

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
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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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	2	8846112		2014-09-30	Baldassarre	
	3	8293284		2012-10-23	Baldassare	
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	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)	☐
	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)	☐

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	Art Unit	1613
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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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	16	Hoeper et al., " Definitions and Diagnosis of Pulmonary Hypertension," Journal of the American College of Cardiology, 62(25):D42-50 (October 2013)	☐
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	18	Royster et al., "Differences in Pulmonary Artery Wedge Pressures Obtained by Balloon Inflation versus Impaction Techniques," Anesthesiology, 61:339-341 (February 1984)	☐

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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)		
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	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

Examiner Signature		Date Considered	

*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.

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.**

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.

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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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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	

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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.

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United States Patent and Trademark Office
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Alexandria, Virginia 22313-1450
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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<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.

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

23338612.doc

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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.

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: Mail **Mail Stop ISSUE FEE**
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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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Fish & Richardson PC
P.O.Box 1022
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

Attorney Docket No.: 26047-0003011 / Client Ref: 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	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 (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

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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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	=								
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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 RULE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
14/454,373	08/07/2014	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.

U.S. Patent and Trademark Office

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

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

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

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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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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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]

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

	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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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	

*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.

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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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☐ 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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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.

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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.

23074806.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.

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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 ≥ 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%.

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

or

2) a decrease in PVRI ≥ 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.

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[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%)

[redacted]

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.

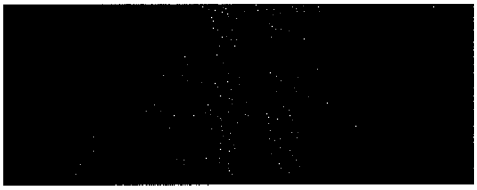
11. REFERENCE LIST

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

[redacted]

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

or

2) a decrease in PVRI ≥ 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

Therapeutics

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.

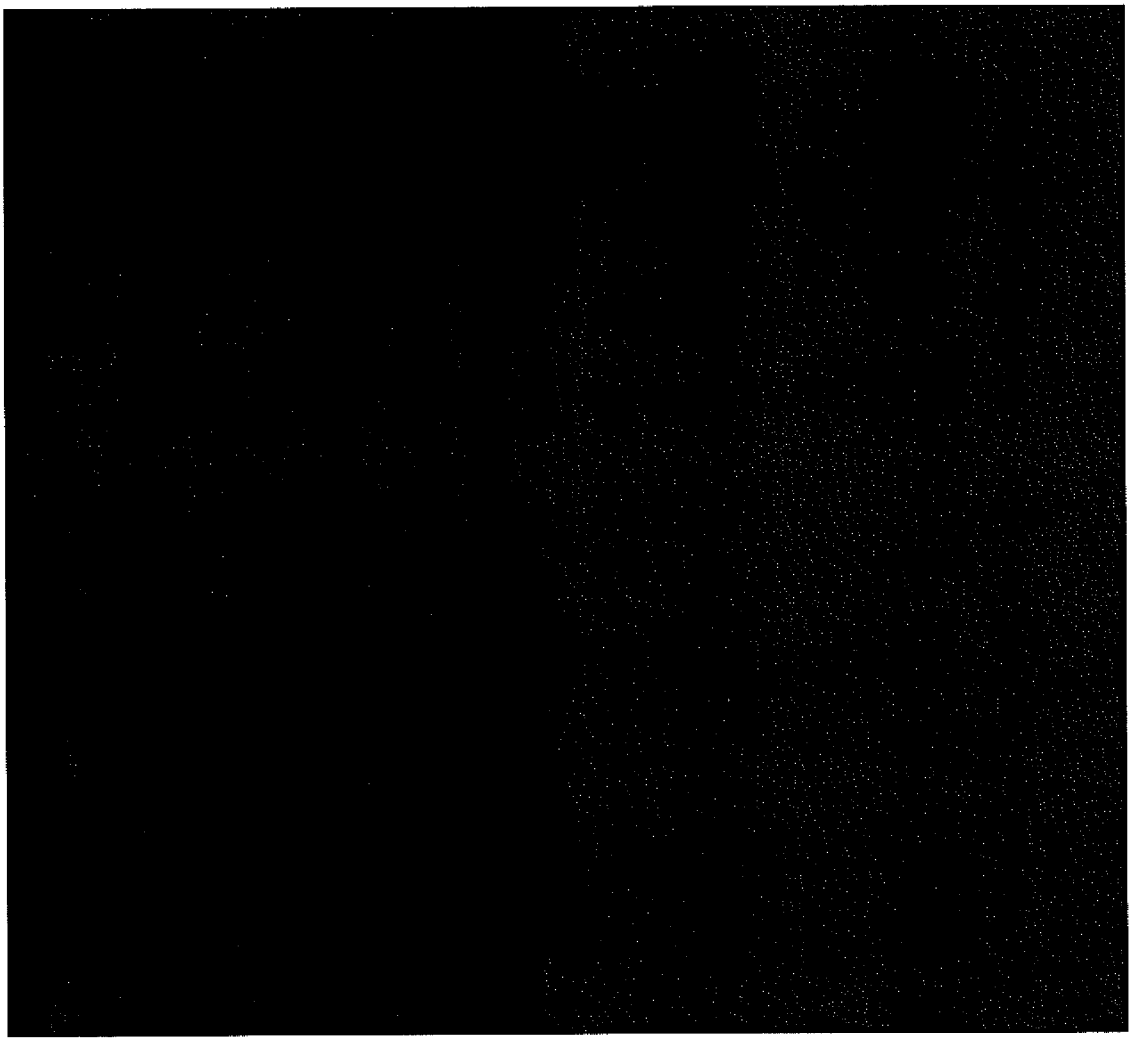
For ease of review, a detailed list of all revisions to this amended protocol is included in appendix 4 of the appended protocol.

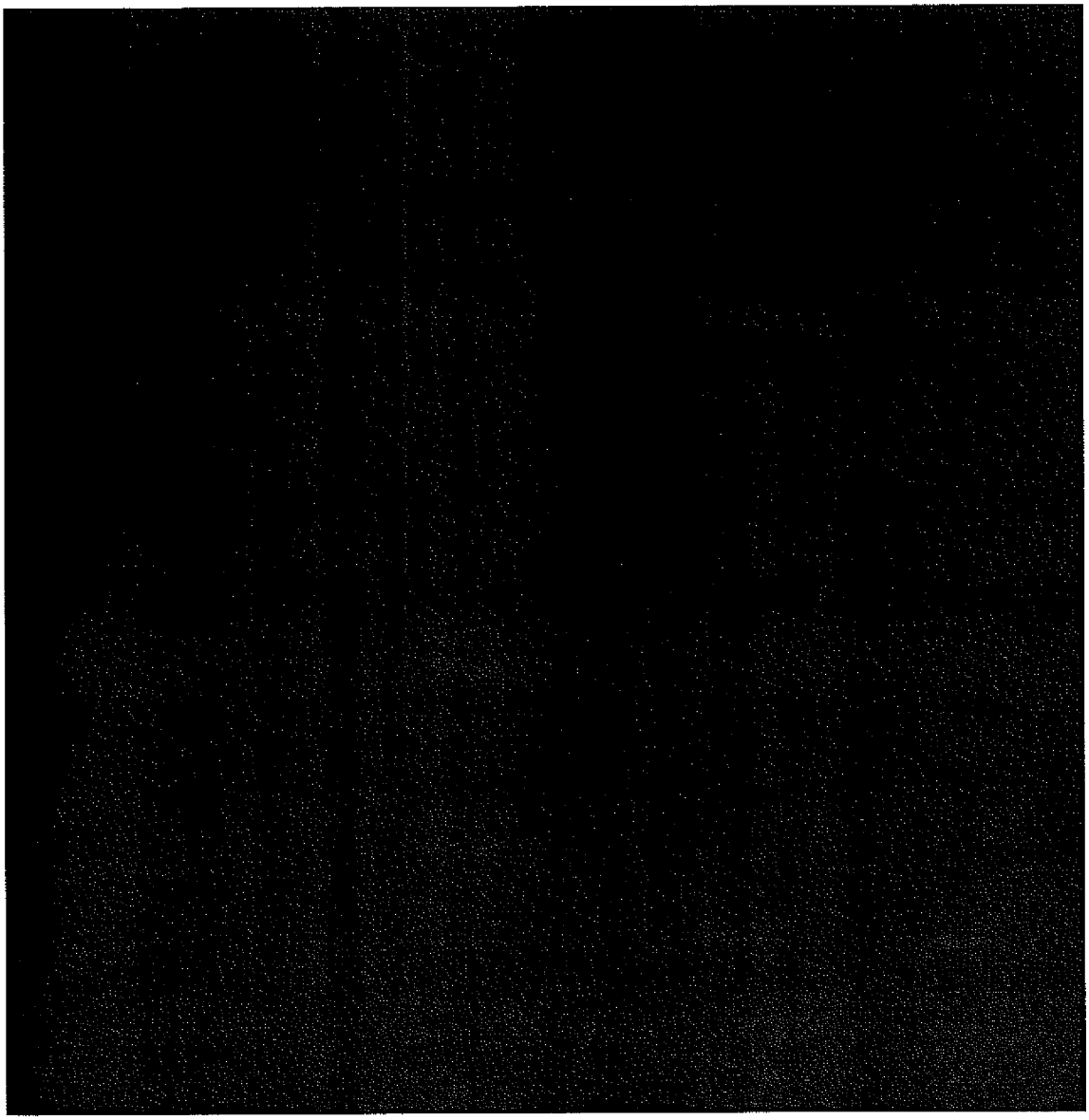
Prior to enrollment of subjects under Amendment 2, further revisions were made to the protocol resulting in Amendment 3.

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>>

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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

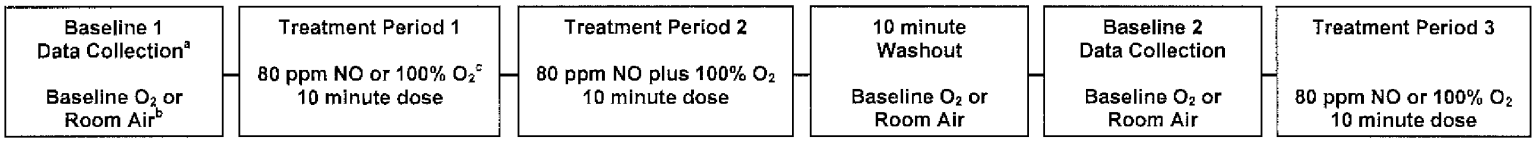
discontinued and the facemask removed according to standard medical care and hospital specific protocol.

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



[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

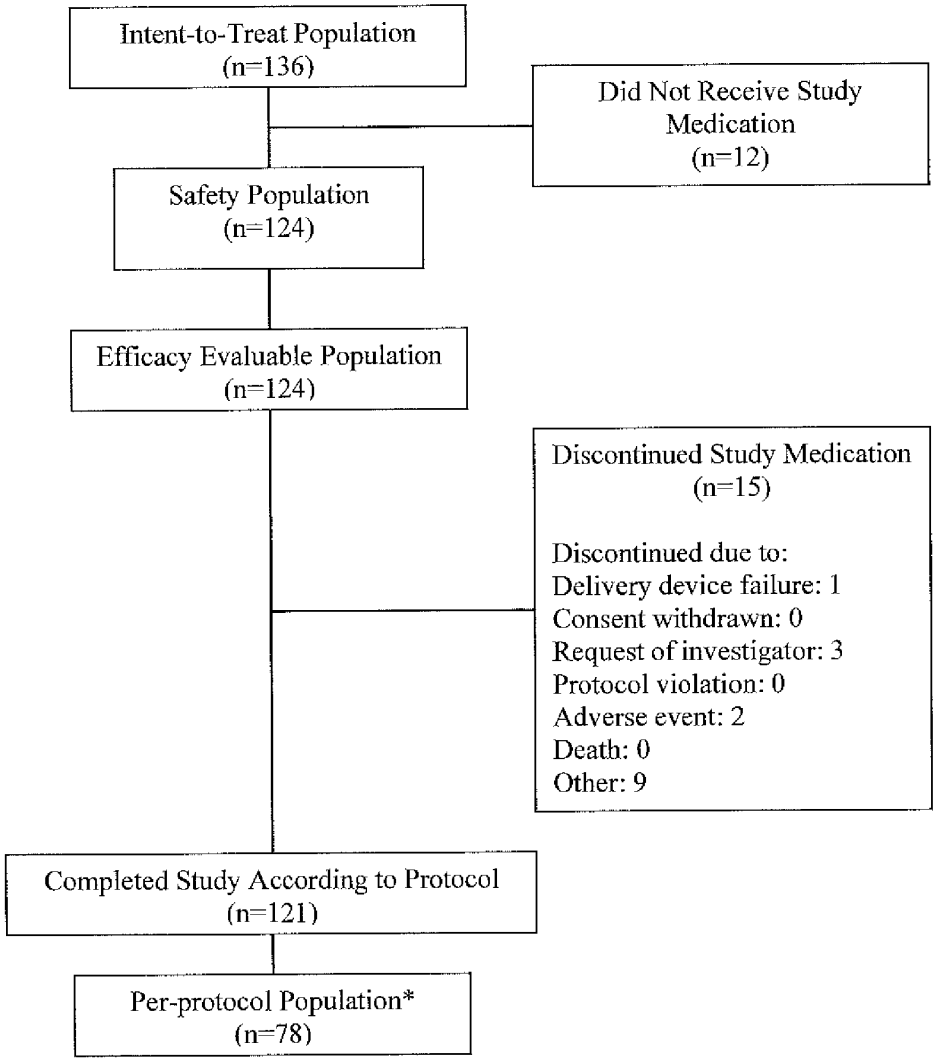
There were no significant changes in the planned conduct of the study or in any analyses.

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·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.

Figure 3: PVRI Change From Baseline By Treatment Group (Intent-to-Treat)

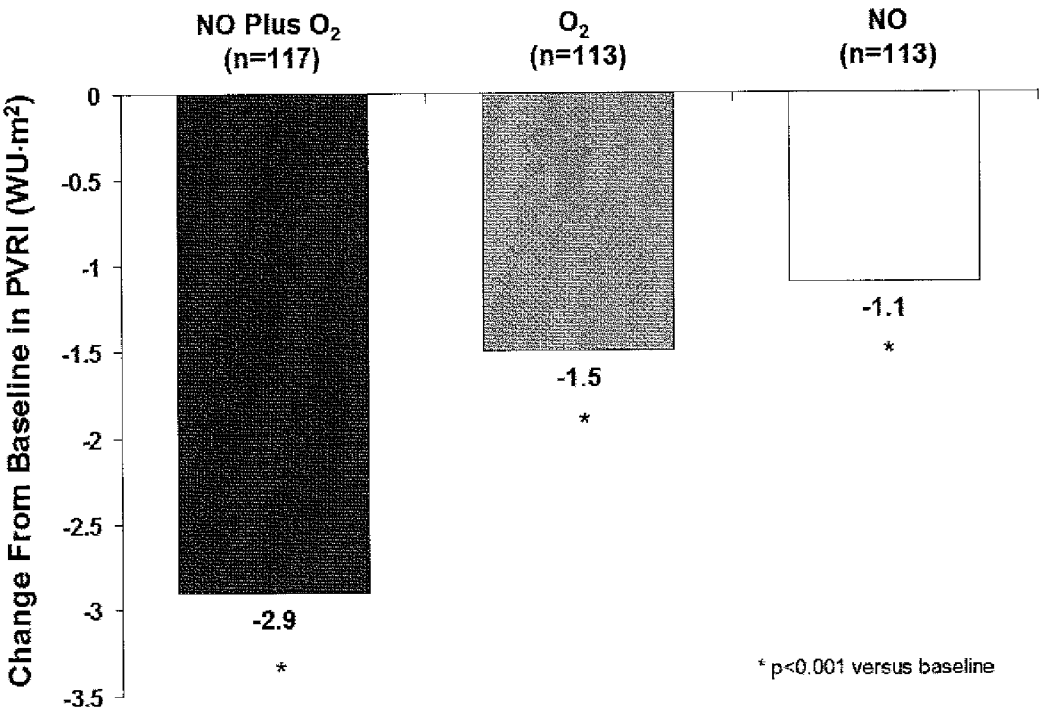


Table 15: PVRI Change From Baseline By Treatment (Intent-to-Treat)

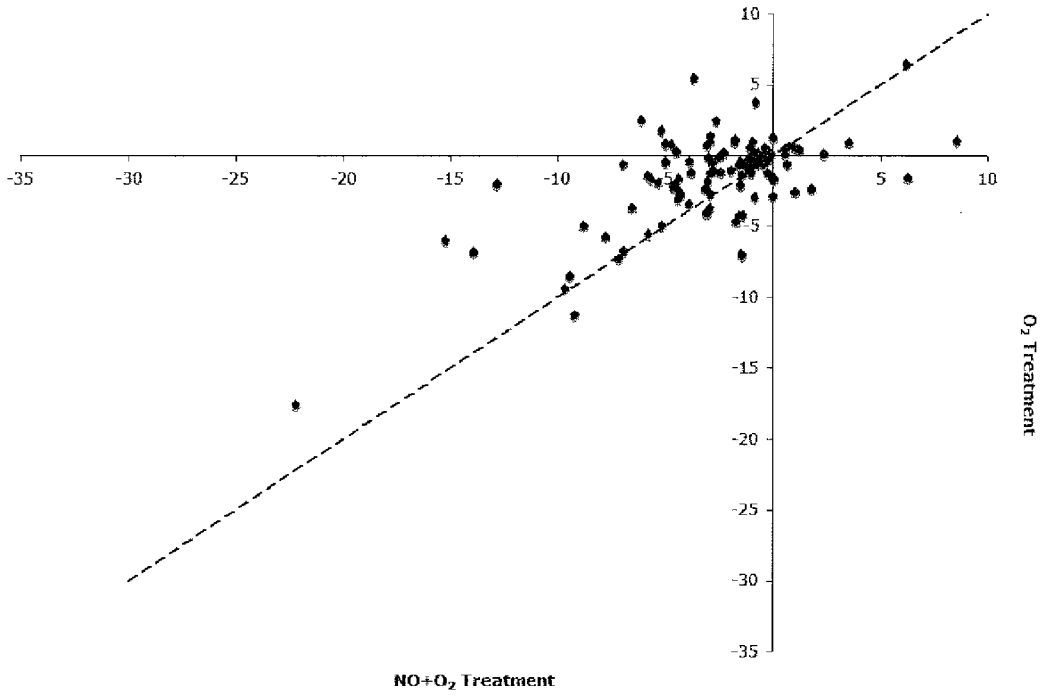
	Treatment		
PVRI ($WU \cdot m^2$)	**NO Plus O_2 (n=117)**	**O_2 (n=113)**	**NO (n=113)**
Baseline (room air)			
Mean	10.8	10.0	10.3
SD	10.30	9.65	10.33
Median	7.5	6.9	6.6
Minimum, maximum	0.5, 54.0	0.5, 47.7	0.9, 54.0
Post-treatment			
Mean	7.8	8.5	9.2
SD	8.75	8.63	10.45
Median	3.6	5.5	5.6
Minimum, maximum	0.0, 44.8	0.5, 36.5	-6.3, 55.3
Change From Baseline			
Mean	-2.9	-1.5	-1.1
SD	4.75	3.13	3.04
Median	-1.8	-0.7	-0.8
Minimum, maximum	-31.2, 8.6	-17.6, 6.5	-10.0, 5.3
p-value[a]	<0.001	<0.001	<0.001
Pairwise comparisons NO plus O_2 versus O_2, p<0.001 NO plus O_2 versus NO, p<0.001 O_2 versus NO, p=0.171			

[a] p-value from a Wilcoxen Signed Rank test. Only patients with data to determine response at both treatments are included in this analysis.

Source: Section 14.2.2, Table 6.1.1 and Appendix 16.2.6

Results for the per-protocol population supported those for the intent-to-treat population. In the per-protocol population, the mean changes from baseline with NO plus O_2, O_2 and NO were -3.8 (p<0.001), -1.9 (p<0.001), and -1.1 (p=0.025) $WU \cdot m^2$, respectively.

Figure 4: PVRI Change From Baseline NO Plus O_2 Versus O_2 Alone (Intent-to-Treat)



The mean percent changes from baseline in PVRI for the intent-to-treat population (Table 16 and Figure 5) were -29.6%, -15.2%, and -15.9% for NO plus O2, O2, and NO, respectively (all p<0.001 versus baseline).

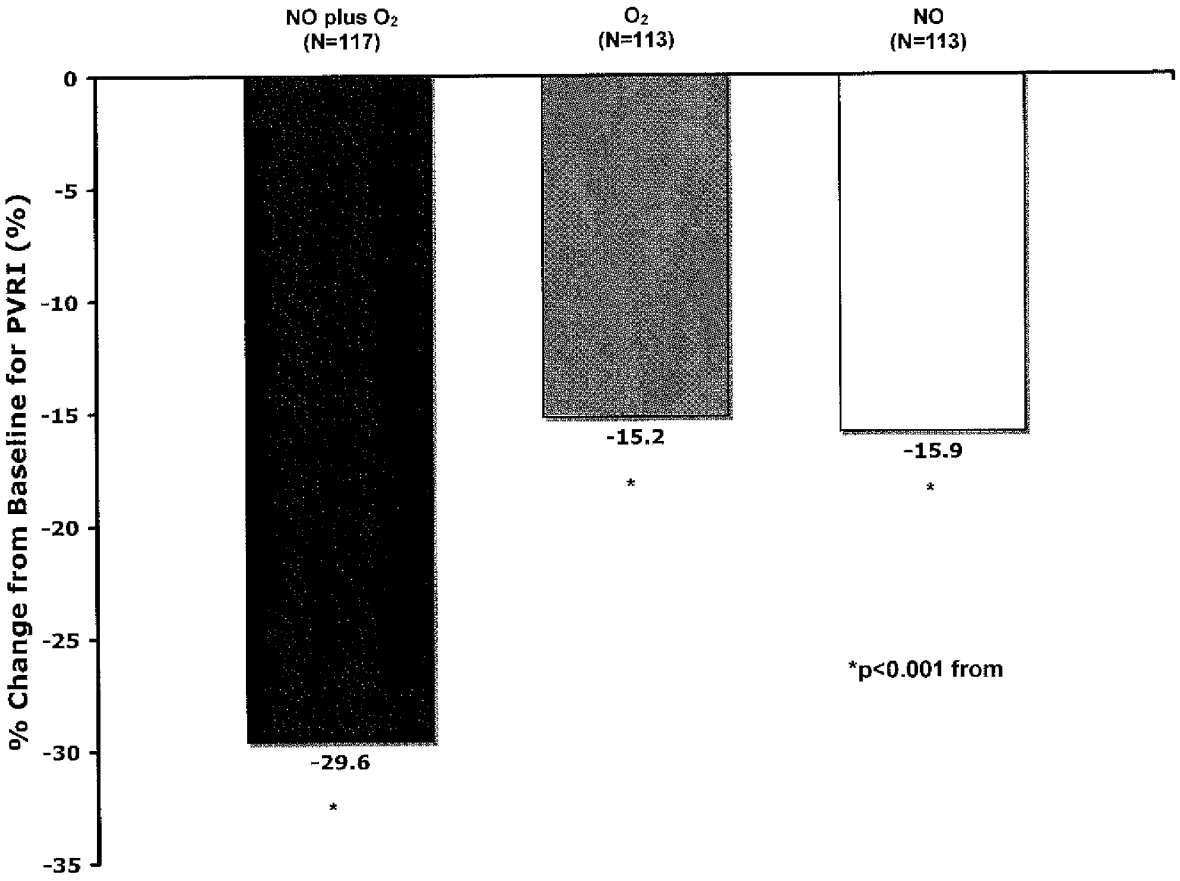
Table 16: PVRI Percent Change From Baseline By Treatment (Intent-to-Treat)

	Treatment		
PVRI ($WU \cdot m^2$)	**NO Plus O_2 (n=117)**	**O_2 (n=113)**	**NO (n=113)**
Baseline (room air)			
Mean	10.8	10.0	10.3
SD	10.30	9.65	10.33
Median	7.5	6.9	6.6
Minimum, maximum	0.5, 54.0	0.5, 47.7	0.9, 54.0
Post-treatment			
Mean	7.8	8.5	9.2
SD	8.75	8.63	10.45
Median	3.6	5.5	5.6
Minimum, maximum	0.0, 44.8	0.5, 36.5	-6.3, 55.3
Percent Change From Baseline			
Mean	-29.6	-15.2	-15.9
SD	38.74	29.23	43.35
Median	-30.8	-14.8	-15.5
Minimum, maximum	-102.7, 201.1	-73.1, 89.7	-270.7, 117.7
p-value[a]	<0.001	<0.001	<0.001
Pairwise comparisons NO plus O_2 versus O_2, p=0.001 NO plus O_2 versus NO, p=0.002 O_2 versus NO, p=0.915			

[a] p-value from a Wilcoxen Signed Rank test. Only patients with data to determine response at both treatments are included in this analysis.

Source: Section 14.2.2, Table 6.1.3 and Appendix 16.2.6

Figure 5: PVRI Percent Change From Baseline by Treatment (Intent-to-Treat)



The mean percent changes from baseline in PVRI for the per-protocol population were -26.7% ($p<0.001$), -12.5% ($p<0.001$), and -7.8% ($p = 0.011$), respectively, for NO plus O_2, O_2, and NO.

Changes from baseline in PVRI for patients without shunts in both the intent-to-treat and the per-protocol populations were generally consistent with those for all patients in the respective populations.

Percent changes from baseline in PVRI for patients without shunts in both the intent-to-treat and the per-protocol populations were generally consistent with those for all patients in the respective populations.

All treatments also significantly decreased PAPm in the intent-to-treat population (Table 17). The mean changes from baseline in PAPm were -7.1, -3.5, and -4.1 mm Hg for NO plus O_2, O_2, and NO, respectively (all $p<0.001$ versus baseline).

Table 17: PAPm Change From Baseline By Treatment (Intent-to-Treat)

	Treatment		
PAPm (mm Hg)	**NO Plus O_2 (n=124)**	**O_2 (n=121)**	**NO (n=120)**
Baseline (room air)			
Mean	45.3	44.2	45.0
SD	16.78	16.30	17.57
Median	41.8	41.7	40.7
Minimum, maximum	17.0, 93.0	16.7, 88.7	14.0, 113.0
Post-treatment			
Mean	38.3	40.7	41.0
SD	16.38	14.57	17.94
Median	34.7	38.7	37.2
Minimum, maximum	12.7, 84.0	26.0, 85.0	16.0, 89.0
Change From Baseline			
Mean	-7.1	-3.5	-4.1
SD	8.25	8.10	7.51
Median	-5.3	-2.3	-2.8
Minimum, maximum	-36.0	-37.3, 17.7	-50.3, 9.0
p-value[a]	<0.001	<0.001	<0.001
Pairwise comparisons NO plus O_2 versus O_2, p<0.001 NO plus O_2 versus NO, p<0.001 O_2 versus NO, p=0.637			

[a] p-value from a Wilcoxen Signed Rank Test. Only patients with data to determine response at both treatments are included in this analysis.

Source: Section 14.2.2, Table 6.2.1 and Appendix 16.2.6

All treatments also significantly decreased PAPm in the per-protocol population. The mean changes from baseline in PAPm were -7.6, -4.2, and -3.8 mm Hg for NO plus O_2, O_2, and NO, respectively (all p<0.001 versus baseline).

Results for patients without shunts in the intent-to-treat and per-protocol populations generally matched those for all patients in the respective populations.

Results for the intent-to-treat population indicated no differences among treatments with respect to changes from baseline in CO (Table 18). The mean changes from baseline in CO were 0.0 mL/minute for each treatment.

Table 18: CO Change From Baseline By Treatment (Intent-to-Treat)

	Treatment		
CO (mL/minute)	**NO Plus O_2 (n=112)**	**O_2 (n=109)**	**NO (n=109)**
Baseline (room air)			
Mean	2.3	2.2	2.3
SD	1.43	1.37	1.35
Median	1.9	1.9	2.0
Minimum, maximum	-2.5, 6.8	-2.5, 5.9	0.4, 6.8
Post-treatment			
Mean	2.2	2.2	2.4
SD	1.29	1.27	1.34
Median	2.0	1.9	2.0
Minimum, maximum	0.2, 6.4	0.4, 5.1	0.4, 7.4
Change From Baseline			
Mean	0.0	0.0	0.0
SD	1.01	0.70	0.88
Median	-0.1	-0.1	0.0
Minimum, maximum	-5.7, 5.1	-2.9, 4.6	-5.5, 4.5
p-value[a]	0.049	0.132	0.614
Pairwise comparisons NO plus O_2 versus O_2, p=0.979 NO plus O_2 versus NO, p=0.267 O_2 versus NO, p=0.259			

[a] p-value from a Wilcoxen Signed Rank Test. Only patients with data to determine response at both treatments are included in this analysis.

Source: Section 14.2.2, Table 6.3.1 and Appendix 16.2.6

Results for the per-protocol population also indicated no differences among treatments with respect to changes from baseline in CO. The mean changes from baseline in CO were 0.0 mL/minute for each treatment.

Results for patients without shunts in the intent-to-treat and per-protocol populations generally matched those for all patients in the respective populations.

Results for the intent-to-treat population indicated that treatment with NO plus O_2 and O_2 alone significantly increased SVRI (Table 19). The change from baseline for NO plus O_2 was 1.4 WU·m^2 (p = 0.007) and that for O_2 was 1.3 WU·m^2 (p = 0.004). The change from baseline in SVRI with NO was -0.2 WU·m^2 (p = 0.889).

Table 19: SVRI Change From Baseline By Treatment (Intent-to-Treat)

	Treatment		
SVRI (WU·m^2)	**NO Plus O_2 (n=109)**	**O_2 (n=106)**	**NO (n=106)**
Baseline (room air)			
Mean	17.2	17.6	18.0
SD	8.86	9.22	8.44
Median	15.9	16.1	16.2
Minimum, maximum	-7.6, 55.6	-7.6, 55.6	1.9, 44.8
Post-treatment			
Mean	18.7	18.9	17.8
SD	9.04	8.78	9.40
Median	17.1	17.1	15.4
Minimum, maximum	3.0, 47.4	3.9, 43.6	3.3, 50.7
Change From Baseline			
Mean	1.4	1.3	-0.2
SD	5.94	5.16	4.65
Median	1.2	1.0	0.2
Minimum, maximum	-20.5, 19.1	-18.1, 17.7	-12.5, 12.7
p-value[a]	0.007	0.004	0.899
Pairwise comparisons NO plus O_2 versus O_2, p=0.952 NO plus O_2 versus NO, p=0.014 O_2 versus NO, p=0.017			

[a] p-value from a Wilcoxen Signed Rank Test. Only patients with data to determine response at both treatments are included in this analysis.

Source: Section 14.2.2, Table 6.4.1 and Appendix 16.2.6

Results for the per-protocol population supported those for the intent-to-treat population. In this population, treatment with NO plus O_2 and O_2 alone also significantly increased SVRI. The change from baseline for NO plus O_2 was 1.5 WU·m^2 ($p = 0.037$) and that for O_2 was 1.4 WU·m^2 ($p = 0.012$). The change from baseline in SVRI with NO was 0.3 WU·m^2 ($p = 0.425$).

Effects of treatment on CO in patients without shunts in the intent-to-treat and per-protocol populations were similar to those for all patients in the respective study populations.

Treatment with NO plus O_2 resulted in a significantly lower PAPm to MAP ratio than O_2 alone (Table 20). These values were 0.60 and 0.64, respectively, for NO plus O_2 and O_2 only ($p<0.001$).

First Table added per request – (Table20b from e-mail)

Table 20: Percent Change in Ratio of PVRI to SVRI by Treatment (Intent-to-Treat)

	Treatment		
Ratio PVRI/SVRI	**NO Plus O_2 (n=108)**	**O_2 (n=105)**	**NO (n=106)**
Baseline			
Mean	0.6	0.5	0.6
SD	0.60	0.45	0.56
Median	0.5	0.5	0.4
Minimum, Maximum	-1.6, 4.7	-1.6, 1.8	0.0, 4.7
Post Treatment			
Mean	0.4	0.4	0.5
SD	0.31	0.31	0.46
Median	0.3	0.4	0.3
Minimum, Maximum	0.0, 1.3	0.0, 1.4	-1.2, 2.2
Percent Change from Baseline			
Mean	-33.5	-19.3	-6.2
SD	36.11	34.59	64.04
Median	-34.0	-21.3	-13.8
Minimum, Maximum	-122.2, 140.1	-122.7, 93.3	-256.1, 294.1
P Value[1]	< 0.001	< 0.001	0.006

1 Wilcoxon Signed Rank Test
Source: Deb to confirm

2nd Table Added: (Table 20a from e-mail)

Table 220: Change in Ratio of PVRI to SVRI by Treatment (Intent-to-Treat)

	Treatment		
Ratio PVRI/SVRI	**NO Plus O_2 (n=108)**	**O_2 (n=105)**	**NO (n=106)**
Baseline			
Mean	0.6	0.5	0.6
SD	0.60	0.45	0.56
Median	0.5	0.5	0.4
Minimum, Maximum	-1.6, 4.7	-1.6, 1.8	0.0, 4.7
Post Treatment			
Mean	0.4	0.4	0.5
SD	0.31	0.31	0.46
Median	0.3	0.4	0.3
Minimum, Maximum	0.0, 1.3	0.0, 1.4	-1.2, 2.2
Change from Baseline			
Mean	-0.2	-0.1	-0.1
SD	0.52	0.31	0.54
Median	-0.1	-0.1	0.0
Minimum, Maximum	-4.4, 2.0	-1.6, 2.0	-4.4, 1.6
P Value[1]	< 0.001	< 0.001	0.002

1 Wilcoxon Signed Rank Test
Source: Deb to confirm

There was no difference in the PAPm to MAP ratios for NO plus O_2 and O_2 alone in the per-protocol population. This value was 0.71 for both NO plus O_2 and O_2 only ($p = 0.094$).

Results for patients without shunts in the intent-to-treat and per-protocol populations were consistent with those from all patients in the respective populations.

11.4.4. Statistical/Analytical Issues

11.4.4.1. Adjustments for Covariates

No adjustments were made for covariates.

11.4.4.2. Handling of Dropouts or Missing Data

There was no imputation of missing data. For the tabulations of demographics and efficacy statistics, patients with missing data were not included in the denominator for the calculation of any frequency percentages.

The denominator for concomitant medications and all adverse events was the total number of patients in the treatment group, regardless of any missing data.

11.4.4.3. Interim Analyses and Data Monitoring

Interim analyses for this study were performed periodically for the Steering Committee to review.

11.4.4.4. Multicenter Studies

No adjustments in the data analysis were made with respect to this variable.

11.4.4.5. Multiple Comparisons/Multiplicity

No adjustments for multiple comparisons are necessary. The primary efficacy analysis was performed on the primary endpoint comparing the two treatment groups of interest. Other statistical tests to compare other treatment groups and secondary endpoints are provided as supportive data only.

11.4.4.6. Use of an "Efficacy Subset" of Patients

Intent-to-treat patients were all patients randomized regardless of actual receipt of any treatment gas, the treatment gas actually received, or the appropriateness of their enrollment. Efficacy analyses were also performed on the per-protocol population, since > 5% of the patients had baseline pulmonary vascular resistance index (PVRI) > 3 $WU \cdot m^2$ and actually took study medication. The per-protocol population included all patients who took study medication and had baseline PVRI >3 $WU \cdot m^2$.

11.4.4.7. Active-Control Studies Intended to Show Equivalence

This study had an active comparator, but was not intended to show equivalence.

11.4.4.8. Examination of Subgroups

There was no significant difference in pulmonary vasoreactivity for patients without shunts versus the entire study group in either the intent-to-treat or per-protocol populations. This was also the case for all secondary efficacy variables.

11.4.5. Tabulation of Individual Response Data

[To be provided]

11.4.6. Drug Dose, Drug Concentration, and Relationship to Response

Not applicable

11.4.7. Drug-Drug and Drug-Disease Interactions

Not applicable

11.4.8. By-Patient Displays

[To be provided]

11.4.9. Efficacy Conclusions

Results for the primary efficacy variable indicated that for the intent-to-treat population, NO plus O_2 resulted in a significantly higher pulmonary vasoreactivity response rate (25.7%) versus O_2 only (14.7%) ($p = 0.019$). In addition, 17.4% of patients responded only to NO plus O_2 versus 6.4% who responded to O_2 only.

A considerable proportion of randomized patients (36.6%) did not meet the entry criteria for PVRI > 3 units at baseline. For this reason, a per-protocol analysis was performed as well. For each of the pairwise comparisons noted above, the treatment effect was of similar or greater magnitude and in the same direction as for the ITT population. These results were generally not statistically significant due to the smaller sample size.

We note that seven patients (6.4%) responded to 100% O_2 but **did not** respond to NO 80 ppm with 90% O_2, which seems illogical. These seven patients were reviewed individually.

Table 21: Patients that responded only to 100% Oxygen

Pt Number	%Δ PVRI **O_2**	%Δ PVRI **O_2+NO**	%Δ PVRI **NO**	Comment
1004	-58.6%	-39.9%	+51.7%	CI -5.2%

Pt Number	%Δ PVRI O_2	%Δ PVRI O_2+NO	%Δ PVRI NO	Comment
1015	-25.6%	-27.3%	+10.57%	CI -7.0%
1026	-42.8%	-19.2%	+61.5%	2nd baseline very high
2007	-25.7%	-73.3%	-39.6%	CI -25.91%
3006	-45.9%	+48.2%	+117.7	BL PVRI 1.33
6005	-39.5	-55.5	-10.8	mPAP -19.4%
10003	-32.6	-6.7	+10.45%	

- Patient 1004 was a 5-month-old baby boy with a 39.9% reduction in PVRI on the combination regimen, but dropped the CI by 5.2%, greater than the 5% limit set by the response criteria. In absolute terms, this was a reduction of CI from 8.65 to 8.11 L/m/M^2, which is within the measurement error of the procedure[14].
- Patient 1015 was an 8.7-year-old girl with a 27.3% reduction in PVRI, but dropped the CI by 7.0% (1.95 to 1.81 L/m/M^2).
- Patient 1026 was a 2 ½-month-old baby girl that had O_2 alone in the third treatment period. In this patient, the second baseline value for PVRI (prior to the O_2 alone treatment period) was much higher than the initial baseline PVRI (4.525 WU·m^2 vs 6.755 WU·m^2), indicating that the patient was not at baseline when the final PVRI value was obtained.
- Patient 2007 was a 5-month-old baby boy requiring supplemental oxygen at baseline; the patient demonstrated a large decrease in PVRI and PAP, but a large drop in CI as well, without other obvious explanation.
- Patient 3006 was a 6-month-old baby boy with near-normal PVRI at first baseline (1.334 WU·m^2); this patient had O_2 alone in the first treatment period. In the first period there was a large percentage drop in PVRI, followed by a continual rise in PVRI, accompanied by a decrease in the CI over the subsequent periods. It is not clear if these changes are related to treatment, patient factors or procedural factors.
- Patient 6005 was an 8.6-year-old boy with CHD without a shunt, on supplemental oxygen at baseline. In this case, response criteria require a decrease in PAPm of ≥20%. In this case, the reduction in PVRI was 55.5%, but the reduction in PAPm was 19.4%, less than the 20% criterion.
- Patient 10003 was a 10.6-year-old boy on supplemental oxygen at baseline. This patient met response criteria to O_2 alone in the first period, without response to the other treatments in period 2 and period 3, without other obvious explanation.

Looking at these patients individually, we see that 4 of the 7 had more than adequate reduction in PVRI or PAP to qualify as responders to NO with O_2 but missed other elements of the response criteria; one patient was not at equilibrium during the procedure, and 2 are unexplained. There do

not appear to be commonalities among these patients with regard to center, diagnosis, age, race or sequence of treatment. None of these patients reported an AE.

There was no significant difference between pulmonary vasoreactivity response rates for NO alone versus O_2 alone in the intent-to-treat population (23.6% versus 15.1%, p=0.117), although numerically more patients were responders with NO alone as compared with O_2 alone. For this comparison, 19.8% of patients responded only to NO versus 11.3% for O_2 only. Comparison of results for NO and NO plus O_2 in the intent-to-treat population also indicated no significant differences in pulmonary vasoreactivity response. The response rate for NO was 24.1% and that for NO plus O_2 was 26.8% (p=0.602). In this comparison, 13.9% of patients responded only to NO versus 16.7% for NO plus O_2.

There was no significant difference in pulmonary vasoreactivity among patients with or without shunts, with or without intubation (an indicator of general anesthesia rather than simple sedation), in either the intent-to-treat or per-protocol populations. In the intent-to-treat population, 45.9% of patients with shunts responded versus 46.2% of those without shunts (p=1.000). There was no appreciable difference in response rates by treatment in patients with or without shunts. Patients with cardiomyopathy as the primary diagnosis seemed to respond more often than those with IPAH or CHD, but the number of those patients is too small to influence the overall results.

All treatments significantly decreased PVRI. 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·m^2, respectively (all p<0.001 versus baseline). The mean percent changes from baseline in PVRI for the intent-to-treat population were -29.6%, -15.2%, and -15.9% for NO plus O_2, O_2, and NO, respectively (all p<0.001 versus baseline).

All treatments also significantly decreased PAPm in the intent-to-treat population. The mean changes from baseline in PAPm were -7.1, -3.5, and -4.1 mm Hg for NO plus O_2, O_2, and NO, respectively (all p<0.001 versus baseline).

In the intent-to-treat population, there were no differences in mean changes from baseline in CO (0.0 mL/minute for each treatment).

Results for the intent-to-treat population indicated that treatment with NO plus O_2 and O_2 alone significantly increased SVRI. The change from baseline for NO plus O_2 was 1.4 WU·m^2 (p=0.007) and that for O_2 was 1.3 WU·m^2 (p=0.004). The change from baseline in SVRI with NO was -0.2 WU·m^2 (p=0.899). Given the decrease in PAPm, this suggests that inhaled NO, alone or with O_2 is selective for the pulmonary vascular bed. This is further reflected in the change in ratio between the PA pressures and the systemic pressures. Treatment with NO plus O_2 resulted in a significantly lower PAPm to MAP ratio than O_2 alone. These values were 0.62 and 0.66 for NO plus O_2 and O_2 only (p=0.001). The reduction from baseline in the ratio of PAPm to MAP for NO with O_2 is 17.7%, as compared with a reduction of 10.6% and 7.8% for O_2 alone and NO alone, respectively. Thus we can conclude that inhaled nitric oxide (alone or with oxygen) is a selective pulmonary vasodilator. Not confirmed – DR.

12. SAFETY EVALUATION

12.1. Extent of Exposure

Exposure to NO plus O_2, NO, and O_2 is summarized in Table 4. The mean durations of exposure to NO plus O_2, NO, and O_2 were 15.5 minutes, 15.3 minutes, and 15.9 minutes, respectively.

12.2. Adverse Events

12.2.1. Brief Summary of Adverse Events

Seven patients experienced AEs during this study. These included cardiac arrest, bradycardia, low CO output syndrome, elevated ST segment on the ECG, decreased O_2 saturation, hypotension, mouth hemorrhage, and PH.

12.2.2. Display of Adverse Events

12.2.2.1. All-causality Adverse Events

Seven patients experienced AEs during this study (Table 22). These included cardiac arrest, bradycardia, low CO output syndrome, elevated ST segment on the ECG, decreased O_2 saturation, hypotension, mouth hemorrhage, and PH. The numbers of patients and events are too small to determine whether risk for AEs differed by diagnosis.

Table 22: Adverse Events By Diagnosis (Safety)

	Diagnosis			
System Organ Class/Preferred Term (n [%])[a]	**IPAH (n=28)**	**Cardiomyopathy (n=5)**	**CHD (n=91)**	**Overall (n=124)**
Patients With at Least One AE	0 (0.0)	1 (20.0)	6 (6.6)	7 (5.6)
Cardiac Disorders	0 (0.0)	0 (0.0)	3 (3.3)	3 (2.4)
Bradycardia	0 (0.0)	0 (0.0)	2 (2.2)	2 (1.6)
Cardiac Arrest	0 (0.0)	0 (0.0)	1 (1.1)	1 (0.8)
Low CO Syndrome	0 (0.0)	0 (0.0)	1 (1.1)	1 (0.8)
Investigations	0 (0.0)	1 (20.0)	2 (2.2)	3 (2.4
ECG ST Segment Elevation	0 (0.0)	1 (20.0)	0 (0.0)	1 (0.8)
O_2 Saturation Decreased	0 (0.0)	0 (0.0)	2 (2.2)	2 (1.6)
Vascular Disorders	0 (0.0)	0 (0.0)	1 (1.1)	2 (1.6)
Hypotension	0 (0.0)	0 (0.0)	1 (1.1)	2 (1.6)
Gastrointestinal Disorders	0 (0.0)	0 (0.0)	1 (1.1)	1 (0.8)
Mouth Hemorrhage	0 (0.0)	0 (0.0)	1 (1.1)	1 (0.8)
Respiratory, Thoracic, and Mediastinal Disorders	0 (0.0)	0 (0.0)	1 (1.1)	1 (0.8)
PH	0 (0.0)	0 (0.0)	1 (1.1)	1 (0.8)

[a] System organ classes and preferred terms are coded using the MedDRA dictionary. System organ classes and preferred terms are listed in descending order of frequency for the Overall column. A patient with multiple occurrences of an AE is counted only once in the AE category.

Source: Section 14.3.1, Table 8.1 and Appendix 16.2.7

Adverse events are summarized by diagnosis and age in Table 23, diagnosis and gender in Table 24, and diagnosis and race in Table 25. Overall, AEs occurred more often in patients ≤ 10 years of age (6.7%) than in those >10 years old (2.9%). They also occurred more often in whites (9.6%) versus other races (0.0%). Patient gender had no effect on the incidence of adverse events; 4.8% of males and 6.5% of females experienced at least one AE.

Table 23: Adverse Events By Diagnosis and Age (Safety)

	Diagnosis and Age Group							
	IPAH		Cardiomyopathy		CHD		Overall	
System Organ Class/Preferred Term (n [%])[a]	**≤10 years** (n=17)	**>10 Years** (n=11)	**≤10 years** (n=4)	**>10 Years** (n=1)	**≤10 years** (n=68)	**>10 Years** (n=23)	**≤10 years** (n=89)	**>10 Years** (n=35)
Patients With at Least One AE	0 (0.0)	0 (0.0)	1 (25.0)	0 (0.0)	5 (7.4)	1 (4.3)	6 (6.7)	1 (2.9)
Cardiac Disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.9)	1 (4.3)	2 (2.2)	1 (2.9)
Cardiac Arrest	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.5)	0 (0.0)	1 (1.1)	0 (0.0)
Bradycardia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.5)	1 (4.3)	1 (1.1)	1 (2.9)
Low CO Syndrome	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.5)	0 (0.0)	1 (1.1)	0 (0.0)
Gastrointestinal Disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.5)	0 (0.0)	1 (1.1)	0 (0.0)
Mouth Hemorrhage	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.5)	0 (0.0)	1 (1.1)	0 (0.0)
Investigations	0 (0.0)	0 (0.0)	1 (25.0)	0 (0.0)	2 (2.9)	0 (0.0)	3 (3.4)	0 (0.0)
ECG ST Segment Elevation	0 (0.0)	0 (0.0)	1 (25.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.1)	0 (0.0)
O_2 Saturation Decreased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.9)	0 (0.0)	2 (2.2)	0 (0.0)
Respiratory, Thoracic, and Mediastinal Disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.5)	0 (0.0)	1 (1.1)	0 (0.0)
PH	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.5)	0 (0.0)	1 (1.1)	0 (0.0)
Vascular Disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.5)	0 (0.0)	2 (2.2)	0 (0.0)
Hypotension	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.5)	0 (0.0)	2 (2.2)	0 (0.0)

[a] System organ classes and preferred terms are coded using the MedDRA dictionary. System organ classes and preferred terms are listed in descending order of frequency for the Overall column. A patient with multiple occurrences of an AE is counted only once in the AE category.

Source: Section 14.3.1, Table 8.2 and Appendix 16.2.7

Table 24: Adverse Events By Diagnosis and Gender (Safety)

	Diagnosis and Gender							
	IPAH		Cardiomyopathy		CHD		Overall	
System Organ Class/Preferred Term (n [%])[a]	**Male (n=15)**	**Female (n=13)**	**Male (n=3)**	**Female (n=2)**	**Male (n=44)**	**Female (n=47)**	**Male (n=62)**	**Female (n=62)**
Patients With at Least One AE	0 (0.0)	0 (0.0)	0 (0.0)	1 (50.0)	3 (6.8)	3 (6.4)	3 (4.8)	4 (6.5)
Cardiac Disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (4.5)	1 (2.1)	2 (3.2)	1 (1.6)
Bradycardia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.3)	1 (2.1)	1 (1.6)	1 (1.6)
Cardiac Arrest	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.1)	0 (0.0)	1 (1.6)
Low CO Syndrome	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.3)	0 (0.0)	1 (1.6)	0 (0.0)
Gastrointestinal Disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.3)	0 (0.0)	1 (1.6)	0 (0.0)
Mouth Hemorrhage	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.3)	0 (0.0)	1 (1.6)	0 (0.0)
Investigations	0 (0.0)	0 (0.0)	0 (0.0)	1 (50.0)	0 (0.0)	2 (4.3)	0 (0.0)	3 (4.8)
ECG ST Segment Elevation	0 (0.0)	0 (0.0)	0 (0.0)	1 (50.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)
O_2 Saturation Decreased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (4.3)	0 (0.0)	2 (3.2)
Respiratory, Thoracic, and Mediastinal Disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.3)	0 (0.0)	1 (1.6)	0 (0.0)
PH	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.3)	0 (0.0)	1 (1.6)	0 (0.0)
Vascular Disorders	0 (0.0)	0 (0.0)	0 (0.0)	1 (50.0)	0 (0.0)	1 (2.1)	0 (0.0)	2 (3.2)
Hypotension	0 (0.0)	0 (0.0)	0 (0.0)	1 (50.0)	0 (0.0)	1 (2.1)	0 (0.0)	2 (3.2)

[a] System organ classes and preferred terms are coded using the MedDRA dictionary. System organ classes and preferred terms are listed in descending order of frequency for the Overall column. A patient with multiple occurrences of an AE is counted only once in the AE category.

Source: Section 14.3.1, Table 8.3 and Appendix 16.2.7

Table 25: Adverse Events By Diagnosis and Race (Safety)

	Diagnosis and Race							
	IPAH		Cardiomyopathy		CHD		Overall	
System Organ Class/Preferred Term (n [%])[a]	**White (n=19)**	**All Other (n=9)**	**White (n=3)**	**All Other (n=2)**	**White (n=51)**	**All Other (n=40)**	**White (n=73)**	**All Other (n=51)**
Patients With at Least One AE	0 (0.0)	0 (0.0)	1 (33.3)	0 (0.0)	6 (11.8)	0 (0.0)	7 (9.6)	0 (0.0)
Cardiac Disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (5.9)	0 (0.0)	3 (4.1)	0 (0.0)
Bradycardia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (3.9)	0 (0.0)	2 (2.7)	0 (0.0)
Cardiac Arrest	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	0 (0.0)	1 (1.4)	0 (0.0)
Low CO Syndrome	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	0 (0.0)	1 (1.4)	0 (0.0)
Gastrointestinal Disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	0 (0.0)	1 (1.4)	0 (0.0)
Mouth Hemorrhage	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	0 (0.0)	1 (1.4)	0 (0.0)
Investigations	0 (0.0)	0 (0.0)	1 (33.3)	0 (0.0)	2 (3.9)	0 (0.0)	3 (4.1)	0 (0.0)
ECG ST Segment Elevation	0 (0.0)	0 (0.0)	1 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.4)	0 (0.0)
O_2 Saturation Decreased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (3.9)	0 (0.0)	2 (2.7)	0 (0.0)
Respiratory, Thoracic, and Mediastinal Disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	0 (0.0)	1 (1.4)	0 (0.0)
PH	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	0 (0.0)	1 (1.4)	0 (0.0)
Vascular Disorders	0 (0.0)	0 (0.0)	1 (33.3)	0 (0.0)	1 (2.0)	0 (0.0)	2 (2.7)	0 (0.0)
Hypotension	0 (0.0)	0 (0.0)	1 (33.3)	0 (0.0)	1 (2.0)	0 (0.0)	2 (2.7)	0 (0.0)

[a] System organ classes and preferred terms are coded using the MedDRA dictionary. System organ classes and preferred terms are listed in descending order of frequency for the Overall column. A patient with multiple occurrences of an AE is counted only once in the AE category.

Source: Section 14.3.1, Table 8.4 and Appendix 16.2.7

12.2.2.2. Adverse Events Related to Study Drug

A total of four patients had AEs that were related to study drug (Table 26). These events included bradycardia, low CO syndrome, ST segment elevation on the ECG, low O_2 saturation, PH, and hypotension.

Table 26: Adverse Events Related to Study Drug By Diagnosis (Safety)

	Diagnosis			
System Organ Class/Preferred Term (n [%])[a]	**IPAH (n=28)**	**Cardiomyopathy (n=5)**	**CHD (n=91)**	**Overall (n=124)**
Patients With at Least One AE Related to Study Drug	0 (0.0)	1 (20.0)	3 (3.3)	4 (3.2)
Cardiac Disorders	0 (0.0)	0 (0.0)	2 (2.2)	2 (1.6)
Bradycardia	0 (0.0)	0 (0.0)	1 (1.1)	1 (0.8)
Low CO Syndrome	0 (0.0)	0 (0.0)	1 (1.1)	1 (0.8)
Investigations	0 (0.0)	1 (20.0)	1 (1.1)	2 (1.6)
ECG ST Segment Elevation	0 (0.0)	1 (20.0)	0 (0.0)	1 (0.8)
O_2 Saturation Decreased	0 (0.0)	0 (0.0)	1 (1.1)	1 (0.8)
Respiratory, Thoracic, and Mediastinal Disorders	0 (0.0)	0 (0.0)	1 (1.1)	1 (0.8)
PH	0 (0.0)	0 (0.0)	1 (1.1)	1 (0.8)
Vascular Disorders	0 (0.0)	1 (20.0)	0 (0.0)	1 (0.8)
Hypotension	0 (0.0)	1 (20.0)	0 (0.0)	1 (0.8)

[a] System organ classes and preferred terms are coded using the MedDRA dictionary. System organ classes and preferred terms are listed in descending order of frequency for the Overall column. A patient with multiple occurrences of an AE is counted only once in the AE category.

Source: Section 14.3.1, Table 10.1 and Appendix 16.2.7

Treatment-related AEs are summarized by diagnosis and age in Table 27. Overall, treatment-related AEs occurred more often in patients ≤ 10 years of age than in those >10 years old. However, there were only four treatment-related AEs, so any conclusions regarding effects of age must be viewed as highly speculative.

Table 27: Adverse Events Related to Study Drug By Diagnosis and Age (Safety)

	Diagnosis and Age Group							
	IPAH		Cardiomyopathy		CHD		Overall	
System Organ Class/Preferred Term (n [%])[a]	≤10 years (n=17)	>10 Years (n=11)	≤10 years (n=4)	>10 Years (n=1)	≤10 years (n=68)	>10 Years (n=23)	≤10 years (n=89)	>10 Years (n=35)
Patients With at Least One AE Related to Study Drug	0 (0.0)	0 (0.0)	1 (25.0)	0 (0.0)	2 (2.9)	1 (4.3)	3 (3.4)	1 (2.9)
Cardiac Disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.5)	1 (4.3)	1 (1.1)	1 (2.9)
Bradycardia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.3)	0 (0.0)	1 (2.9)
Low CO Syndrome	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.5)	0 (0.0)	1 (1.1)	0 (0.0)
Investigations	0 (0.0)	0 (0.0)	1 (25.0)	0 (0.0)	1 (1.5)	0 (0.0)	2 (2.2)	0 (0.0)
ECG ST Segment Elevation	0 (0.0)	0 (0.0)	1 (25.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.1)	0 (0.0)
O_2 Saturation Decreased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.5)	0 (0.0)	1 (1.1)	0 (0.0)
Respiratory, Thoracic, and Mediastinal Disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.5)	0 (0.0)	1 (1.1)	0 (0.0)
PH	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.5)	0 (0.0)	1 (1.1)	0 (0.0)
Vascular Disorders	0 (0.0)	0 (0.0)	1 (25.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.1)	0 (0.0)
Hypotension	0 (0.0)	0 (0.0)	1 (25.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.1)	0 (0.0)

[a] System organ classes and preferred terms are coded using the MedDRA dictionary. System organ classes and preferred terms are listed in descending order of frequency for the Overall column. A patient with multiple occurrences of an AE is counted only once in the AE category.

Source: Section 14.3.1, Table 10.2 and Appendix 16.2.7

Treatment-related AEs are summarized by diagnosis and gender in Table 28. Two treatment-related AEs occurred in males (3.2%) and two in females (3.2%).

Table 28: Adverse Events Related to Study Drug by Diagnosis and Gender (Safety)

	Diagnosis and Gender							
	IPAH		Cardiomyopathy		CHD		Overall	
System Organ Class/Preferred Term (n [%])[a]	**Male (n=15)**	**Female (n=13)**	**Male (n=3)**	**Female (n=2)**	**Male (n=44)**	**Female (n=47)**	**Male (n=62)**	**Female (n=62)**
Patients With at Least One AE Related to Study Drug	0 (0.0)	0 (0.0)	0 (0.0)	1 (50.0)	2 (4.5)	1 (2.1)	2 (3.2)	2 (3.2)
Cardiac Disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (4.5)	0 (0.0)	2 (3.2)	0 (0.0)
Bradycardia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.3)	0 (0.0)	1 (1.6)	0 (0.0)
Low CO Syndrome	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.3)	0 (0.0)	1 (1.6)	0 (0.0)
Investigations	0 (0.0)	0 (0.0)	0 (0.0)	1 (50.0)	0 (0.0)	1 (2.1)		2 (3.2)
ECG ST Segment Elevation	0 (0.0)	0 (0.0)	0 (0.0)	1 (50.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)
O_2 Saturation Decreased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.1)	0 (0.0)	1 (1.6)
Respiratory, Thoracic, and Mediastinal Disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.3)	0 (0.0)	1 (1.6)	0 (0.0)
PH	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.3)	0 (0.0)	1 (1.6)	0 (0.0)
Vascular Disorders	0 (0.0)	0 (0.0)	0 (0.0)	1 (50.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)
Hypotension	0 (0.0)	0 (0.0)	0 (0.0)	1 (50.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)

[a] System organ classes and preferred terms are coded using the MedDRA dictionary. System organ classes and preferred terms are listed in descending order of frequency for the Overall column. A patient with multiple occurrences of an AE is counted only once in the AE category.

Source: Section 14.3.1, Table 10.3 and Appendix 16.2.7

Treatment-related AEs are summarized by diagnosis and race in Table 29. All four treatment-related AEs occurred in whites (5.5%).

Table 30: Adverse Events Related to Study Drug By Diagnosis and Race (Safety)

	Diagnosis and Race							
	IPAH		Cardiomyopathy		CHD		Overall	
System Organ Class/Preferred Term (n [%])[a]	White (n=19)	All Other (n=9)	White (n=3)	All Other (n=2)	White (n=51)	All Other (n=40)	White (n=73)	All Other (n=51)
Patients With at Least One AE Related to Study Drug	0 (0.0)	0 (0.0)	1 (33.3)	0 (0.0)	3 (5.9)	0 (0.0)	4 (5.5)	0 (0.0)
Cardiac Disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (3.9)	0 (0.0)	2 (2.7)	0 (0.0)
Bradycardia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	0 (0.0)	1 (1.4)	0 (0.0)
Low CO Syndrome	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	0 (0.0)	1 (1.4)	0 (0.0)
Investigations	0 (0.0)	0 (0.0)	1 (33.3)	0 (0.0)	1 (2.0)	0 (0.0)	2 (2.7)	0 (0.0)
ECG ST Segment Elevation	0 (0.0)	0 (0.0)	1 (33.3)	0 (0.0)	1 (2.0)	0 (0.0)	1 (1.4)	0 (0.0)
O_2 Saturation Decreased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	0 (0.0)	1 (1.4)	0 (0.0)
Respiratory, Thoracic, and Mediastinal Disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	0 (0.0)	1 (1.4)	0 (0.0)
PH	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.4)	0 (0.0)
Vascular Disorders	0 (0.0)	0 (0.0)	1 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.4)	0 (0.0)
Hypotension	0 (0.0)	0 (0.0)	1 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.4)	0 (0.0)

[a] System organ classes and preferred terms are coded using the MedDRA dictionary. System organ classes and preferred terms are listed in descending order of frequency for the Overall column. A patient with multiple occurrences of an AE is counted only once in the AE category.

Source: Section 14.3.1, Table 10.4 and Appendix 16.2.7

12.2.3. Analysis of Adverse Events

All treatments were well-tolerated. Seven patients experienced AEs during this study and four of these were considered treatment-related. The adverse events included cardiac arrest, bradycardia, low CO syndrome, elevated ST segment on the ECG, decreased O_2 saturation, hypotension, mouth hemorrhage, and PH. The numbers of patients and events are too small to determine whether risk for AEs differed by diagnosis, age, gender, or race.

12.2.4. Listing of Adverse Events by Patient

A list of all AEs is provided in Table 30. Four of the seven AEs were mild or moderate in intensity and resolved. There were two severe AEs (low CO syndrome and hypertension, experienced by a single patient) that resulted in death.

Table 31: Adverse Events (Safety)

Patient Number	Age (years)	Race	Adverse Event	Serious	Severity	Relation to Study Drug	Outcome of Event
1007	0.7	White	Mouth hemorrhage	No	Moderate	Remote	Resolved
1020	0.8	White	O_2 saturation decreased	No	Mild	Possible	Resolved
4003	8.4	White	Hypotension	Yes	Moderate	Probable	Resolved
			ST segment elevation	Yes	Moderate	Probable	Resolved
4008	3.4	White	Low CO output syndrome	Yes	Severe	Probable	Fatal
		White	Hypertension	Yes	Severe	Probable	Fatal
6010	0.4	White	Hypotension	No	Mild	Not related	Resolved
17002	15.6	White	Bradycardia	No	Mild	Highly probable	Resolved
			Bradycardia	No	Mild	Highly probable	Resolved
5002	0.3	White	Bradycardia	Yes	Severe	Not related	Fatal
			O_2 saturation decreased	Yes	Severe	Not related	Fatal
			Cardiac arrest	Yes	Severe	Not related	Fatal

Source: Appendix 16.2.7

12.3. Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

12.3.1. Listing of Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

12.3.1.1. Deaths

Narratives for deaths are provided in Section 12.3.2.

12.3.1.2. Other Serious Adverse Events

Table 292: Serious Adverse Events By Diagnosis (Safety)

	Diagnosis			
System Organ Class/Preferred Term (n [%])[a]	**IPAH (n=28)**	**Cardiomyopathy (n=5)**	**CHD (n=91)**	**Overall (n=124)**
Patients With at Least One SAE	0 (0.0)	1 (20.0)	2 (2.2)	3 (2.4)
Cardiac Disorders	0 (0.0)	0 (0.0)	2 (2.2)	2(1.6)
Bradycardia	0 (0.0)	0 (0.0)	1 (1.1)	1 (0.8)
Cardiac Arrest	0 (0.0)	0 (0.0)	1 (1.1)	1 (0.8)
Low CO Syndrome	0 (0.0)	0 (0.0)	1 (1.1)	1 (0.8)
Investigations	0 (0.0)	1 (20.0)	1 (1.1)	2 (1.6)
ECG ST Segment Elevation	0 (0.0)	1 (20.0)	0 (0.0)	1 (0.8)
Oxygen Saturation Decreased	0 (0.0)	0 (0.0)	1 (1.1)	1 (0.8)
Respiratory, Thoracic, and Mediastinal Disorders	0 (0.0)	0 (0.0)	1 (1.1)	1 (0.8)
PH	0 (0.0)	0 (0.0)	1 (1.1)	1 (0.8)
Vascular Disorders	0 (0.0)	1 (20.0)	0 (0.0)	1 (0.8)
Hypotension	0 (0.0)	1 (20.0)	0 (0.0)	1 (0.8)

[a] System organ classes and preferred terms are coded using the MedDRA dictionary. System organ classes and preferred terms are listed in descending order of frequency for the Overall column. A patient with multiple occurrences of an AE is counted only once in the AE category.

Source: Section 14.3.1, Table 9.1 and Appendix 16.2.7

Serious AEs are presented by diagnosis and age, gender, and race in Tables 32, 33, and 34, respectively. Given the fact that only three patients experienced SAEs, no conclusions can be drawn from these analyses.

Table 303: Serious Adverse Events By Diagnosis and Age (Safety)

	Diagnosis and Age Group							
	Idiopathic		Cardiomyopathy		CHD		Overall	
System Organ Class/Preferred Term (n [%])[a]	≤10 years (n=17)	>10 Years (n=11)	≤10 years (n=4)	>10 Years (n=1)	≤10 years (n=68)	>10 Years (n=23)	≤10 years (n=89)	>10 Years (n=35)
Patients With at Least One SAE	0 (0.0)	0 (0.0)	1 (25.0)	0 (0.0)	2 (2.9)	0 (0.0)	3 (3.4)	0 (0.0)
Cardiac Disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.9)	0 (0.0)	2 (2.2)	0 (0.0)
Bradycardia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.5)	0 (0.0)	1 (1.1)	0 (0.0)
Cardiac Arrest	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.5)	0 (0.0)	1 (1.1)	0 (0.0)
Low CO Syndrome	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.5)	0 (0.0)	1 (1.1)	0 (0.0)
Investigations	0 (0.0)	0 (0.0)	1 (25.0)	0 (0.0)	1 (1.5)	0 (0.0)	2 (2.2)	0 (0.0)
ECG ST Segment Elevation	0 (0.0)	0 (0.0)	1 (25.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.1)	0 (0.0)
Oxygen Saturation Decreased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.5)	0 (0.0)	1 (1.1)	0 (0.0)
Respiratory, Thoracic, and Mediastinal Disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.5)	0 (0.0)	1 (1.1)	0 (0.0)
PH	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.5)	0 (0.0)	1 (1.1)	0 (0.0)
Vascular Disorders	0 (0.0)	0 (0.0)	1 (25.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.1)	0 (0.0)
Hypotension	0 (0.0)	0 (0.0)	1 (25.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.1)	0 (0.0)

[a] System organ classes and preferred terms are coded using the MedDRA dictionary. System organ classes and preferred terms are listed in descending order of frequency for the Overall column. A patient with multiple occurrences of an AE is counted only once in the AE category.

Source: Section 14.3.1, Table 9.2 and Appendix 16.2.7

Table 314: Serious Adverse Events By Diagnosis and Gender (Safety)

	Diagnosis and Gender							
	Idiopathic		Cardiomyopathy		CHD		Overall	
System Organ Class/Preferred Term (n [%])[a]	Male (n=15)	Female (n=13)	Male (n=3)	Female (n=2)	Male (n=44)	Female (n=47)	Male (n=62)	Female (n=62)
Patients With at Least One SAE	0 (0.0)	0 (0.0)	0 (0.0)	1 (50.0)	1 (2.3)	1 (2.1)	1 (1.6)	2 (3.2)
Cardiac Disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.3)	1 (2.1)	1 (1.6)	1 (1.6)
Bradycardia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.1)	0 (0.0)	1 (1.6)
Cardiac Arrest	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.1)	0 (0.0)	1 (1.6)
Low CO Syndrome	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.3)	0 (0.0)	1 (1.6)	0 (0.0)
Investigations	0 (0.0)	0 (0.0)	0 (0.0)	1 (50.0)	0 (0.0)	1 (2.1)	0 (0.0)	2 (3.2)
ECG ST Segment Elevation	0 (0.0)	0 (0.0)	0 (0.0)	1 (50.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)
Oxygen Saturation Decreased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.1)	0 (0.0)	1 (1.6)
Respiratory, Thoracic, and Mediastinal Disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.3)	0 (0.0)	1 (1.6)	0 (0.0)
PH	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.3)	0 (0.0)	1 (1.6)	0 (0.0)
Vascular Disorders	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.5)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)
Hypotension	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.5)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)

[a] System organ classes and preferred terms are coded using the MedDRA dictionary. System organ classes and preferred terms are listed in descending order of frequency for the Overall column. A patient with multiple occurrences of an AE is counted only once in the AE category.

Source: Section 14.3.1, Table 9.3 and Appendix 16.2.7

Table 325: Serious Adverse Events By Diagnosis and Race (Safety)

	Diagnosis and Race							
	Idiopathic		Cardiomyopathy		CHD		Overall	
System Organ Class/Preferred Term (n [%])[a]	White (n=19)	All Other (n=9)	White (n=3)	All Other (n=2)	White (n=51)	All Other (n=40)	White (n=73)	All Other (n=51)
Patients With at Least One SAE	0 (0.0)	0 (0.0)	1 (33.3)	0 (0.0)	2 (3.9)	0 (0.0)	3 (4.1)	0 (0.0)
Cardiac Disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (3.9)	0 (0.0)	2 (2.7)	0 (0.0)
Bradycardia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	0 (0.0)	1 (1.4)	0 (0.0)
Cardiac Arrest	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	0 (0.0)	1 (1.4)	0 (0.0)
Low CO Syndrome	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	0 (0.0)	1 (1.4)	0 (0.0)
Investigations	0 (0.0)	0 (0.0)	1 (33.3)	0 (0.0)	1 (2.0)	0 (0.0)	2 (2.7)	0 (0.0)
ECG ST Segment Elevation	0 (0.0)	0 (0.0)	1 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.4)	0 (0.0)
Oxygen Saturation Decreased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	0 (0.0)	1 (1.4)	0 (0.0)
Respiratory, Thoracic, and Mediastinal Disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	0 (0.0)	1 (1.4)	0 (0.0)
PH	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	0 (0.0)	1 (1.4)	0 (0.0)
Vascular Disorders	0 (0.0)	0 (0.0)	1 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.4)	0 (0.0)
Hypotension	0 (0.0)	0 (0.0)	1 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.4)	0 (0.0)

[a] System organ classes and preferred terms are coded using the MedDRA dictionary. System organ classes and preferred terms are listed in descending order of frequency for the Overall column. A patient with multiple occurrences of an AE is counted only once in the AE category.

Source: Section 14.3.1, Table 9.4 and Appendix 16.2.7

12.3.1.3. Other Significant Adverse Events

Two patients withdrew from treatment due to AEs (Table 35). Treatment was stopped in one patient due to decreased O_2 saturation (possibly related to study treatment) and in a second patient due to hypotension and ST segment elevation (probably related to study treatment).

Table 33: Adverse Events Leading to Withdrawal From Treatment (Safety)

Adverse Event	Number of Patients (%) (n=124)
Cardiovascular	1 (0.8)
Hypotension and ST Segment Elevation	1 (0.8)
Investigations	1 (0.8)
O_2 Saturation Decreased	1 (0.8)

Source: Appendix 16.2.7

12.3.2. Narratives of Deaths, Other Serious Adverse Events, and Certain Other Significant Adverse Events

12.3.2.1. Deaths

Patient 04-001 ([redacted]S1000863) (Hypotension, cardiac arrest) was a 2-year, 6-month-old male. As a neonate, the patient had coarctation of the aorta requiring surgery by means of the Waldhausen technique. He was followed 5 months later with percutaneous angioplasty for recoarctation, with good hemodynamic results. Two years later, the patient suffered severe symptoms of low CO and was diagnosed with severe mitral stenosis. Surgical implantation of a mechanical mitral prosthetic valve had no beneficial effect, and the patient experienced severe left ventricular dysfunction in the postoperative period. The patient was transferred for evaluation of pulmonary resistances and the conditions for heart transplantation, and was entered into the present study. The patient received NO 80 ppm for 79 minutes. Thirty minutes after withdrawal of study medication, the patient suffered hypotension, bradycardia, hypoxemia, and cardiac arrest. A cardiac massage and dobutamine infusion were initiated; the patient recovered the normal rhythm and normal tension values in 15 minutes. He was transferred to the intensive care unit. Treatment with dobutamine, sildenafil, and sedation was maintained during the next 72 hours. Catheterization was repeated the next day to reevaluate the pulmonary resistances; NO was administered with a hospital device, outside the study protocol, with an oral loading dose of sildenafil. There was no response in pulmonary pressure, and the patient died 8 hours after the procedure in the intensive care unit with refractory hypotension. During and after the study, the patient received the following concomitant medications: sevoflurane, rocuronium bromide, fentanyl citrate, dobutamine, milrinone, sildenafil, ranitidine, cefazolin, acetaminophen, enoxaparin, and midazolam. The investigator deemed this event to be unrelated to study medication.

Patient 04-008 ([redacted]S10000682) (Pulmonary Hypertension, Hypotension, Hypoxemia, Bradycardia) was a 4-year-old male with a history of congenital heart disease, increased right ventricular pressure, ventricular septal defect repair, pulmonary artery stenosis, transposition of the great vessels, balloon atrial septostomy, pulmonary hypertension, Eisenmenger's syndrome, and dilatation of the right ventricle and right-to-left shunt across the small residual ventricular septal defect. He underwent a cardiac catheterization for pulmonary artery stenosis. During the procedure a very high pressure was found in both pulmonary branches with a transpulmonary gradient increase. The patient received NO 80 ppm for a total of 70 minutes. Between the first and second segment of the protocol (O_2 100% and NO 80 ppm) the patient was accidentally extubated and the investigator delayed the collection of data 40 minutes until the child recovered the hemodynamic and gasometric stability. During the last phase of the protocol, while receiving NO alone, the patient experienced severe hypotension with hypoxemia and bradycardia. The protocol was discontinued, and the patient was treated with dobutamine and 100% O_2. There was an initial improvement in O_2 saturation; arterial tension and sinus rhythm recovery were obtained. The patient was transferred to the intensive care unit. During the following hours, he suffered a severe deterioration with PH and right ventricular failure. Despite administration of 100% O_2, NO at 20 ppm, and other therapies (rocuronium bromide, atropine, dobutamine, milrinone, dopamine, vecuronium, epinephrine, sildenafil, fentanyl, ceftazidime, teicoplanin, furosemide, NO, and hyperventilation), the patient expired the next day after atrial fibrillation.

Performed on Day 1, echocardiography results showed increased right ventricular pressure in the last month; chest x-ray results showed no pleural effusion, and laboratory tests showed the following values: Hgb 12 g/dL; platelets 301,000/μL; leukocytes 9.1 x 10^3/mm^3; neutrophils 60.5%; glucose 272 mg/dL; urea 39 mg/dL; calcium 9.2 mg/dL; alanine aminotransferase 16 U/L; and aspartate aminotransferase 19 U/L. The investigator deemed this event to have a probable relation to the study drug.

Patient 05-002 ([redacted]S1000062) (Hypoxia/Bradycardia) was a 4-month-old female with a history of congenital heart disease (atrioventricular septal defect) and secondary pulmonary hypertension. One and a half hours after the start of catheterization, the posterior aortic cusp was accidentally perforated, resulting in moderate aortic regurgitation. When the procedure was completed, the patient was extubated and began to breathe on her own. Post-procedure testing showed the following values: platelets 269,000/μL; pH 7.41; Hgb 10.2 g/dL; erythrocytes 3.00 x 10^6/μL; and hematocrit 31.8%. Two hours after the procedure was completed, the patient suffered oxygen desaturation and severe bradycardia. She required cardiopulmonary resuscitation, which was unsuccessful. Forty minutes later the patient expired. The patient received the following additional concomitant medications: atropine, sevoflurane, fentanyl citrate, and thiopental sodium. Postmortem examination showed hepatization of the lungs, cardiomegaly in the presence of atrioventricular septal defect, severe atrioventricular valve insufficiency, and iatrogenic perforation of the posterior aortic cusp. The investigator judged that subjecting the patient to 100% O_2 for 10 minutes (the first dose) followed by nitric oxide at 80 ppm and 100% O_2 for 10 minutes (the second dose) significantly unbalanced her cardiac output, which led in turn to a severe drop in PVR (from 708 to 88 mm Hg), massive blood overflow to the lungs, and a severe reduction in CO. The investigator, noting that this patient had structural cardiopathy, atrioventricular septal defect, severe pulmonary vascular hypertension, severe atrioventricular valve insufficiency, and moderate aortic regurgitation, judged that "a confluence of different factors" had caused this child's progressive deterioration and death and deemed this event to be unrelated to study medication. However, the medical monitor deemed this event to be possibly related to study medication.

12.3.2.2. Nonfatal Serious Adverse Events * ADD statement: re:Protocol language re: SAE collection up to 12 hours (p.38;Sec.10.4.2) not collected on CRF or Clin database but collected in pharmacovigilance database

Patient 02-002 ([redacted]S1000794) (Pulmonary edema) was a 10-month-old male with a history of mitral regurgitation and PH. After the cardiac catheterization, the patient experienced pulmonary edema, probably due to the administration of contrast for angiography in the setting of severe mitral regurgitation with pulmonary hypertension. The patient was managed in the intensive care unit with mechanical ventilation and improved within 48 hours. He was discharged to the floor after 3 days. The patient received the following additional concomitant medications on the day of therapy: heparin, atracurium besylate, cefamandole, and alfentanil hydrochloride. The investigator deemed this event to be unrelated to study medication.

Patient 07-003 ([redacted]S1000682) (Cardiac arrest) was a 14-year-old female with a history of primary pulmonary hypertension, epilepsy, asthma, von Willebrand's disease, and Factor V Leiden deficiency. Eighty minutes post cardiac catheterization, the patient required

cardiopulmonary resuscitation for 90 seconds due to bradycardia down to 42 beats per minute. She required high ventilatory pressure and was treated with NO and transferred to the pediatric intensive care unit, where she experienced three more episodes of hypertension and required short boluses of adrenaline and cardiopulmonary resuscitation overnight. Thirteen days after the event, she was successfully weaned off nitric oxide, and was extubated on the following day. She was diagnosed with von Willebrand's disease and factor V Leiden deficiency. Five weeks after the event, the patient was transferred to another facility for a full assessment of her pulmonary hypertension. She has remained stable with no major concerns, and has recovered almost completely (psychologically and physically) from her cardiac arrest. Seven weeks after the event, she was discharged to home. Confirmatory laboratory tests included electrocardiogram, echocardiogram, electroencephalogram, and an angiogram. The electrocardiogram showed normal sinus rhythm with signs of right ventricular hypertrophy and repolarization abnormalities. The echocardiogram showed normal atrioventricular and ventricular arterial connections; the left ventricle had normal dimensions and function and a shortening fraction of 39.5%; the right ventricle appeared to be slightly dilated and mildly hypertrophic but had preserved its function, although the contractility was sluggish. The electroencephalogram was within normal limits, and the angiogram shown mild enlargement of central pulmonary arteries. On the day that study therapy was administered, the patient received the following additional concomitant medications: vecuronium bromide, propofol, ondansetron, paracetamol, and sodium chloride compound injection. Additionally, the patient received concomitant therapy with the following medicinal products from an unknown starting date until the present date: epoprostenol sodium, sildenafil, lamotrigine, and warfarin. The investigator deemed this event to have a possible relation to the study drug.

Patient 17-001 ([redacted]S1000083) (Hypoxia) was an 8-year-old male with a history of pulmonary hypertension, asthma, adrenal insufficiency, and aorticopulmonary window. The patient completed the study without an adverse event. The physician decided to address the recent history of hemoptysis. An ascending aorta/aortic arch angiogram was performed. No large collaterals were identified off the aortic arch or right or left mammary arteries. In the mid-thoracic and descending aorta, some large anteroposterior and several tiny anteroposterior collaterals were found. Coil closure of the large anteroposterior collaterals was performed. The patient was stable, and sheaths were removed with good hemostasis. Approximately 3.5 hours later, the patient complained of right chest pain (10 on a scale of 10). Heart rate was 99 beats per minute, respiratory rate was 28, and temperature was 37.1°C. Oxygen saturation was 71%. He was treated with acetaminophen for pain and chest pain was reported as 2 on a scale of 10. His O_2 saturation continued to decrease (64-68%) despite oxygen at 2 L via nasal cannula. He was placed on a nonrebreather mask. He became cyanotic, with stridor, and nausea with emesis. He was given ondansetron hydrochloride and intravenous fluids. The patient was transferred to the pediatric intensive care unit for closer monitoring. Stress steroids were given at 19 mg every 6 hours, sildenafil 5 mg every 6 hours, ondansetron as needed, and oxygen to maintain O_2 saturation level >70%. The patient was also receiving ongoing treatment with the following additional concomitant medications: digoxin, bosentan, esomeprazole magnesium, fluticasone propionate, hydrocortisone acetate, montelukast sodium, and ipratropium bromide. The patient was discharged from the hospital in good health 2 days after the event. The investigator deemed the events to be possibly related to a combination of inadequate steroids for adrenal insufficiency and the use of intravenous dye. His pain was judged likely to be related to the anteroposterior

coil placement. The investigator deemed the hypoxia to be unlikely to be related to study medication.

12.3.2.3. Discontinuations Due to Adverse Events

Patient 01-020 (Desaturation during NO administration) was a 1-year-old female with a diagnosis of CHD with pulmonary hypertension and a history of a repaired ventricular septal defect. Seven minutes after initiation of the administration of the third dose of NO, the patient experienced mild systemic desaturation (35%). The protocol was discontinued and the event resolved after 2 minutes. During the study period, the patient received concomitant treatment with intravenous midazolam and nalbuphine hydrochloride. The investigator deemed this event to have a possible relation to the study drug.

Patient 04-003 ([redacted]1000160) (Hypotension, Electrocardiogram ST segment elevation) was an 8.4-year-old female with a history of cardiac valvuloplasty in the neonatal period, aortic stenosis, moderate aortic regurgitation, cardiomyopathy, and pulmonary hypertension. After 4 minutes on NO with 100% O_2 withdrawal, the patient experienced severe systemic hypotension with the same pulmonary pressure and elevation of ST segment in the electrocardiogram. The protocol was discontinued and treatment with 100% O_2 and a dobutamine infusion was initiated. The patient recovered normal pressure in 20 minutes. The patient was intubated and transferred to the pediatric intensive care unit where she was extubated after 8 hours without complications. The patient received the following additional concomitant medications: rocuronium bromide, fentanyl citrate, midazolam, and sevoflurane. The investigator deemed this event to have a probable relation to the study drug.

12.3.3. Analysis and Discussion of Deaths, Other Serious Adverse Events, and Other Significant Adverse Events [redacted]

There was one death considered probably related to two AEs (hypotension and ST segment elevation, both considered to be probably related to study treatment) and two other SAEs in one other patient (low CO syndrome and pulmonary hypertension, both probably related to study treatment) that were not fatal. Treatment was stopped in two patients as a result of AEs. The first patient was the above-described individual who died and the second experienced decreased O_2 saturation considered as possibly related to study drug. Another patient suffered oxygen desaturation and severe bradycardia two hours postprocedure, followed by cardiac arrest and death. Although the investigator cited the patient's numerous underlying cardiovascular conditions in deeming the event unrelated to study medication, the medical monitor considered it possibly related.

12.4. Clinical Laboratory Evaluation

No clinical laboratory evaluation was carried out as part of the safety evaluation for this study.

12.5. Vital Signs, Physical Findings, and Other Observations Related to Safety

Table 34: Vital signs - HR Change From Baseline By Treatment (Intent-to-Treat)

	Treatment		
HR (beats/minute)	**NO Plus O_2 (n=124)**	**O_2 (n=121)**	**NO (n=120)**
Baseline (room air)			
Mean	105.8	105.7	106.6
SD	28.84	30.33	30.72
Median	104.5	102.0	103.5
Minimum, maximum	51.0, 168.0	39.0, 168.0	51.0, 180.0
Post-treatment			
Mean	104.1	102.8	105.9
SD	33.02	30.76	31.57
Median	97.5	97.0	100.0
Minimum, maximum	45.0, 192.0	53.0, 165.0	46.0, 179.0
Change From Baseline			
Mean	-1.7	-2.8	-0.8
SD	13.69	11.35	9.47
Median	-3.0	-3.0	0.0
Minimum, maximum	-38.0, 41.0	-33.0, 38.0	-36.0, 28.0
p-value[a]	0.173	0.007	0.382

[a] p-value from a t-test. Only patients with baseline and post-treatment data are included in the analysis.
Source: Section 14.3.4, Table 11.1.1 and Appendix 16.2.9

NO plus O_2 and O_2 slightly increased SAP in both the intent-to-treat (Table 37) and per-protocol populations. The increase for NO plus O_2 was statistically significant in the per-protocol population (2.9 mm Hg, p=0.028). Treatment with NO slightly increased SAP in the intent-to-treat population and decreased it in the per-protocol population.

Table 35: Vital signs - SAP Change From Baseline By Treatment (Intent-to-Treat)

	Treatment		
SAP (mm Hg)	**NO Plus O_2 (n=124)**	**O_2 (n=121)**	**NO (n=120)**
Baseline (room air)			
Mean	85.4	85.7	86.7
SD	15.03	15.24	15.17
Median	85.0	85.0	85.5
Minimum, maximum	51.0, 132.0	51.0, 132.0	51.0, 126.0
Post-treatment			
Mean	87.4	87.5	86.1
SD	16.63	17.17	16.90
Median	87.0	88.0	84.0
Minimum, maximum	45.0, 136.0	48.0, 130.0	32.0, 134.0
Change From Baseline			
Mean	2.0	1.8	-0.6
SD	11.42	10.56	8.19
Median	1.0	2.0	1.0
Minimum, maximum	-36.0, 49.0	-32.0, 43.0	-25.0, 17.0
p-value[a]	0.057	0.068	0.430

[a] p-value from a t-test. Only patients with baseline and post-treatment data are included in the analysis.
Source: Section 14.3.4, Table 11.2.1 and Appendix 16.2.9

Table 36: Vital signs - DAP Change From Baseline By Treatment (Intent-to-Treat)

	Treatment		
DAP (mm Hg)	**NO Plus O_2 (n=124)**	**O_2 (n=121)**	**NO (n=120)**
Baseline (room air)			
Mean	47.3	48.0	48.6
SD	12.19	11.90	12.86
Median	47.0	48.0	49.0
Minimum, maximum	23.0, 83.0	25.0, 83.0	19.0, 86.0
Post-treatment			
Mean	48.8	49.9	47.8
SD	12.61	12.21	13.06
Median	50.0	50.0	47.0
Minimum, maximum	24.0, 92.0	24.0, 90.0	22.0, 84.0
Change From Baseline			
Mean	1.4	1.8	-0.8
SD	8.63	7.65	6.56
Median	0.5	2.0	0.0
Minimum, maximum	-23.0, 28.0	-28.0, 21.0	-25.0, 15.0
p-value[a]	0.071	0.009	0.184

[a] p-value from a t-test. Only patients with baseline and post-treatment data are included in the analysis.
Source: Section 14.3.4, Table 11.3.1 and Appendix 16.2.9

12.6. Safety Conclusions

Study treatments had slight and non-clinically significant effects on vital signs, including HR, SAP, and DAP.

There was one death considered related to two AEs (hypotension and ST segment elevation, both considered to be probably related to study treatment) and two other serious AEs in one other patient (low CO output syndrome and pulmonary hypertension, both probably related to study treatment) that were serious, but not fatal. Treatment was stopped in two patients as a result of AEs. The first patient was the above-described individual who died and the second experienced decreased O_2 saturation considered as possibly related to study drug. Another patient suffered oxygen desaturation and severe bradycardia two hours postprocedure, followed by cardiac arrest and death. Although the investigator cited the patient's numerous underlying cardiovascular conditions in deeming the event unrelated to study medication, the medical monitor considered it possibly related.

All treatments were well tolerated and seven patients experienced AEs during this study. These included cardiac arrest, bradycardia, low CO syndrome, elevated ST segment on the ECG, decreased O_2 saturation, hypotension, mouth hemorrhage, and PH. The numbers of patients and events are too small to determine whether risk for AEs differed by treatment, diagnosis, age, gender, or race.

A total of four patients had AEs were related to study drug. These events included bradycardia, low CO syndrome, ST segment elevation on the ECG, low O_2 saturation, PH, and hypotension.

All but two AEs were mild or moderate in intensity and resolved.

Serious adverse events were collected from the start of study treatment until hospital discharge or 24 hours, whichever occurred sooner. Six SAEs were reported. Three of these were fatal SAEs, and 3 were nonfatal. Two of the three fatal SAEs were considered related to therapy, as were 2 of three nonfatal SAEs. The numbers of patients and events are too small to determine whether risk for SAEs differed by treatment, diagnosis, age, gender, or race.

Treatment was stopped in two patients as a result of AEs. The first patient was the above-described individual who died and the second experienced decreased O_2 saturation considered as possibly related to study drug.

We note that two patients developed signs of pulmonary edema.

The overall numbers of SAEs and fatal SAEs are within the range of expected for patients with this degree of cardiopulmonary disease. The overall rate is 6/124 (4.8%). This is comparable to the rate of 6% recently reported by Taylor et al in a very similar cohort of patients.[15]

13. DISCUSSION AND OVERALL CONCLUSIONS

The results from this study showed that NO plus O_2 resulted in a significantly higher pulmonary vasoreactivity response rate (25.7%) 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 responded to O_2 only. The results for the per-protocol population generally supported those for the intent-to-treat population, but the population was smaller and the statistical power was lower due to the high number of protocol violations.

The present findings are consistent with the conclusion that NO plus O_2 is more effective than O_2 alone when used as a pulmonary vasodilator. These results are consistent with those from a smaller study of 46 patients with a broad spectrum of pediatric cardiac disease, including atrial septal defect, complete atrioventricular canal, Shone's syndrome, patent ductus arteriosus, truncus arteriosus, and other conditions. In this study, combining 100% O_2 and 80 ppm NO produced a response of ≥ 20% in PVR in 88% of patients versus 64% for O_2 alone ($p = 0.01$).[11] Other prior studies have also reported differences in responses to NO, O_2, and/or the combination of these treatments.[16-18]

Individually, NO and O_2 produced significant and comparable selective pulmonary vasodilation, and they may do so via different mechanisms. It has been demonstrated that NO produces vasorelaxation via a guanosine monophosphate-mediated pathway,[19] but the mechanisms by which O_2 decreases PVR are not known.[11] The observation in the present and a prior study[11] that some patients responded to one agent, but not the other, suggests that the mechanisms underlying NO- and O_2-induced vasorelaxation may be at least somewhat different.

The ability of NO plus O_2 to detect a higher percentage of patients than O_2 alone is clinically important. Patients who respond to pulmonary vasodilator testing have better outcomes when undergoing repair of congenital heart defects.[20-22] The response to acute vasodilator testing in patients with primary PH is an important marker for survival[23] and may also identify patients suitable for long-term medical therapy.[24, 25]

All treatments delivered in this study were well tolerated and only seven patients experienced AEs. All but two AEs were mild or moderate in intensity and resolved. There were two severe AEs (low CO syndrome and hypertension, experienced by a single patient) that resulted in death. Among the 124 patients who received treatment in this study, six suffered an SAE during or immediately following the procedure, an overall rate of 4.8%. This is within the expected range of SAEs for patients with this degree of cardiopulmonary disease. Results from a series of 75 pediatric patients with PH undergoing cardiac catheterization under anesthesia indicated that resuscitation or death occurred in 6% of patients.[15] 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 function.

All treatments appear to be highly selective for the pulmonary vasculature. In each treatment period, the ratio of PAPm to MAP (and likewise the ratio of PRVI to SVRI) decreases with treatment, indicating a greater decrease in the pulmonary pressure than in the systemic pressures.

This is consistent with the direct delivery of therapy to the lungs. Although there is no internal control for pulmonary selectivity in this study, we may compare the change in the ratio of PAPm/MAP with that seen with systemic therapy with prostacyclin or sildenafil. With these therapies, that ratio is typically unchanged or increased.[26-29]

We note that this study randomized only the first treatment assignment; the second treatment period was the combination treatment, and the final treatment was the individual therapy not given in the first period. This was done for clinical reasons; requiring a third washout and baseline period would have made the procedure unacceptably long, subjecting these patients to additional risk. However, without a completely randomized treatment sequence and separate baseline periods, we cannot completely exclude an interaction of treatment with period. We note that the baseline PVRI was similar in baseline period 1 and baseline period 2. The results appear to be quite robust. The results are consistent with the known mechanism of action, and the study results appear to be fully consistent with both internal and previous reports.

In conclusion, the present results indicate that combination testing with NO plus O_2 provides additional pulmonary vasodilation, can be safely delivered to patients during diagnostic cardiac catheterization, and can rapidly identify patients with pulmonary vasoreactivity who may not be recognized with delivery of O_2 alone.

14. TABLES, FIGURES AND GRAPHS REFERRED TO BUT NOT INCLUDED IN THE TEXT

None

14.1. Demographic Data Summary Figures and Tables

14.2. Efficacy Data Summary Figures and Tables

14.3. Safety Data Summary Figures and Tables

14.3.1. Displays of Adverse Events

14.3.2. Listings of Deaths, Other Serious and Significant Adverse Events

14.3.3. Narratives of Deaths, Other Serious and Certain Other Significant Adverse Events

Narrative Category: <Death, Discontinuation Due to an Adverse Event, SAE>

Identification:

Protocol No.	<insert>
Patient No.	<insert>
Patient Initials	<insert>
Patient DOB	<insert>
Adverse Event	
Treatment	
Relationship to Drug	

Demographics:

Age (at time of event)

Gender

Race

Dosing:

Dose

Route

Duration (until event)

Regimen

Medical History:

Relevant Prior Illnesses

Relevant Prior Medications

Current Medical Status:

Clinical Condition

Disease Being Treated

Relevant Concomitant Illnesses

Relevant Concomitant Medications

Relevant Laboratory Measurements

Description of Event:

14.3.4. Abnormal Laboratory Value Listing

15. REFERENCE LIST

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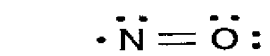
INOmax® (nitric oxide) for inhalation
100 and 800 ppm (parts per million)

DESCRIPTION
INOmax (nitric oxide gas) is a drug administered by inhalation. Nitric oxide, the active substance in INOmax, is a pulmonary vasodilator. INOmax is a gaseous blend of nitric oxide and nitrogen (0.08% and 99.92%, respectively for 800 ppm; 0.01% and 99.99%, respectively for 100 ppm). INOmax is supplied in aluminum cylinders as a compressed gas under high pressure (2000 pounds per square inch gauge [psig]).

The structural formula of nitric oxide (NO) is shown below:



CLINICAL PHARMACOLOGY
Nitric oxide is a compound produced by many cells of the body. It relaxes vascular smooth muscle by binding to the heme moiety of cytosolic guanylate cyclase, activating guanylate cyclase and increasing intracellular levels of cyclic guanosine 3',5'-monophosphate, which then leads to vasodilation. When inhaled, nitric oxide produces pulmonary vasodilation.

INOmax appears to increase the partial pressure of arterial oxygen (PaO_2) by dilating pulmonary vessels in better ventilated areas of the lung, redistributing pulmonary blood flow away from lung regions with low ventilation/perfusion (V/Q) ratios toward regions with normal ratios.

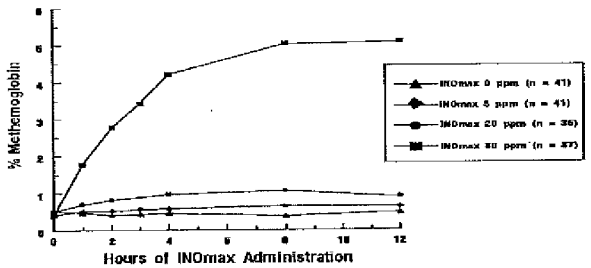
Effects on Pulmonary Vascular Tone in PPHN
Persistent pulmonary hypertension of the newborn (PPHN) occurs as a primary developmental defect or as a condition secondary to other diseases such as meconium aspiration syndrome (MAS), pneumonia, sepsis, hyaline membrane disease, congenital diaphragmatic hernia (CDH), and pulmonary hypoplasia. In these states, pulmonary vascular resistance (PVR) is high, which results in hypoxemia secondary to right-to-left shunting of blood through the patent ductus arteriosus and foramen ovale. In neonates with PPHN, INOmax improves oxygenation (as indicated by significant increases in PaO_2).

PHARMACOKINETICS
The pharmacokinetics of nitric oxide has been studied in adults.

Uptake and Distribution
Nitric oxide is absorbed systemically after inhalation. Most of it traverses the pulmonary capillary bed where it combines with hemoglobin that is 60% to 100% oxygen-saturated. At this level of oxygen saturation, nitric oxide combines predominantly with oxyhemoglobin to produce methemoglobin and nitrate. At low oxygen saturation, nitric oxide can combine with deoxyhemoglobin to transiently form nitrosylhemoglobin, which is converted to nitrogen oxides and methemoglobin upon exposure to oxygen. Within the pulmonary system, nitric oxide can combine with oxygen and water to produce nitrogen dioxide and nitrite, respectively, which interact with oxyhemoglobin to produce methemoglobin and nitrate. Thus, the end products of nitric oxide that enter the systemic circulation are predominantly methemoglobin and nitrate.

Metabolism
Methemoglobin disposition has been investigated as a function of time and nitric oxide exposure concentration in neonates with respiratory failure. The methemoglobin (MetHb) concentration-time profiles during the first 12 hours of exposure to 0, 5, 20, and 80 ppm INOmax are shown in Figure 1.

Figure 1
Methemoglobin Concentration - Time Profiles
Neonates Inhaling 0, 5, 20 or 80 ppm INOmax



Methemoglobin concentrations increased during the first 8 hours of nitric oxide exposure. The mean methemoglobin level remained below 1% in the placebo group and in the 5 ppm and 20 ppm INOmax groups, but reached approximately 5% in the 80 ppm INOmax group. Methemoglobin levels >7% were attained only in patients receiving 80 ppm, where they comprised 35% of the group. The average time to reach peak methemoglobin was 10 ± 9 (SD) hours (median, 8 hours) in these 13 patients; but one patient did not exceed 7% until 40 hours.

Elimination
Nitrate has been identified as the predominant nitric oxide metabolite excreted in the urine, accounting for >70% of the nitric oxide dose inhaled. Nitrate is cleared from the plasma by the kidney at rates approaching the rate of glomerular filtration.

CLINICAL TRIALS
The efficacy of INOmax has been investigated in term and near-term newborns with hypoxic respiratory failure resulting from a variety of etiologies. Inhalation of INOmax reduces the oxygenation index (OI= mean airway pressure in cm H_2O x fraction of inspired oxygen concentration [FiO_2] x 100 divided by systemic arterial concentration in mm Hg [PaO_2]) and increases PaO_2 (See CLINICAL PHARMACOLOGY).

NINOS study
The Neonatal Inhaled Nitric Oxide Study (NINOS) group conducted a double-blind, randomized, placebo-controlled, multicenter trial in 235 neonates with hypoxic respiratory failure. The objective of the study was to determine whether inhaled nitric oxide would reduce the occurrence of death and/or initiation of extracorporeal membrane oxygenation (ECMO) in a prospectively defined cohort of term or near-term neonates with hypoxic respiratory failure unresponsive to conventional therapy. Hypoxic respiratory failure was caused by meconium aspiration syndrome (MAS; 49%), pneumonia/sepsis (21%), idiopathic primary pulmonary hypertension of the newborn (PPHN; 17%), or respiratory distress syndrome (RDS; 11%). Infants ≤14 days of age (mean, 1.7 days) with a mean PaO_2 of 46 mm Hg and a mean oxygenation index (OI) of 43 cm H_2O / mm Hg were initially randomized to receive 100% O_2 with (n=114) or without (n=121) 20 ppm nitric oxide for up to 14 days. Response to study drug was defined as a change from baseline in PaO_2 30 minutes after starting treatment (full response = >20 mm Hg, partial = 10-20 mm Hg, no response = <10 mm Hg). Neonates with a less than full response were evaluated for a response to 80 ppm nitric oxide or control gas. The primary results from the NINOS study are presented in Table 1.

Table 1
Summary of Clinical Results from NINOS Study

	Control (n=121)	NO (n=114)	P value
Death or ECMO*,†	77 (64%)	62 (46%)	0.006
Death	20 (17%)	16 (14%)	0.60
ECMO	66 (55%)	44 (39%)	0.014

* Extracorporeal membrane oxygenation
† Death or need for ECMO was the study's primary end point

Although the incidence of death by 120 days of age was similar in both groups (NO, 14%; control, 17%), significantly fewer infants in the nitric oxide group required ECMO compared with controls (39% vs. 55%, p = 0.014). The combined incidence of death and/or initiation of ECMO showed a significant advantage for the nitric oxide treated group (46% vs. 64%, p = 0.006). The nitric oxide group also had significantly greater increases in PaO_2 and greater decreases in the OI and the alveolar-arterial oxygen gradient than the control group (p<0.001 for all parameters). Significantly more patients had at least a partial response to the initial administration of study drug in the nitric oxide group (66%) than the control group (26%, p<0.001). Of the 125 infants who did not respond to 20 ppm nitric oxide or control, similar percentages of NO-treated (18%) and control (20%) patients had at least a partial response to 80 ppm nitric oxide for inhalation or control drug, suggesting a lack of additional benefit for the higher dose of nitric oxide. No infant had study drug discontinued for toxicity. Inhaled nitric oxide had no detectable effect on mortality. The adverse events collected in the NINOS trial occurred at similar incidence rates in both treatment groups (See ADVERSE REACTIONS). Follow-up exams were performed at 18–24 months for the infants enrolled in this trial. In the infants with available follow-up, the two treatment groups were similar with respect to their mental, motor, audiologic, or neurologic evaluations.

CINRGI study
This study was a double-blind, randomized, placebo-controlled, multicenter trial of 186 term and near-term neonates with pulmonary hypertension and hypoxic respiratory failure. The primary objective of the study was to determine whether INOmax would reduce the receipt of ECMO in these patients. Hypoxic respiratory failure was caused by MAS (35%), idiopathic PPHN (30%), pneumonia/sepsis (24%), or RDS (8%). Patients with a mean PaO_2 of 54 mm Hg and a mean OI of 44 cm H_2O / mm Hg were randomly assigned to receive either 20 ppm INOmax (n=97) or nitrogen gas (placebo; n=89) in addition to their ventilatory support. Patients who exhibited a PaO_2 >60 mm Hg and a pH < 7.55 were weaned to 5 ppm INOmax or placebo. The primary results from the CINRGI study are presented in Table 2.

Table 2
Summary of Clinical Results from CINRGI Study

	Placebo	INOmax	P value
ECMO*,†	51/89 (57%)	30/97 (31%)	<0.001
Death	5/89 (6%)	3/97 (3%)	0.48

* Extracorporeal membrane oxygenation
† ECMO was the primary end point of this study

Significantly fewer neonates in the INOmax group required ECMO compared to the control group (31% vs. 57%, p<0.001). While the number of deaths were similar in both groups (INOmax, 3%; placebo, 6%), the combined incidence of death and/or receipt of ECMO was decreased in the INOmax group (33% vs. 58%, p<0.001).

In addition, the INOmax group had significantly improved oxygenation as measured by PaO_2, OI, and alveolar-arterial gradient (p<0.001 for all parameters). Of the 97 patients treated with INOmax, 2 (2%) were withdrawn from study drug due to methemoglobin levels >4%. The frequency and number of adverse events reported were similar in the two study groups (See ADVERSE REACTIONS).

ARDS study
In a randomized, double-blind, parallel, multicenter study, 385 patients with adult respiratory distress syndrome (ARDS) associated with pneumonia (46%), surgery (33%), multiple trauma (26%), aspiration (23%), pulmonary contusion (18%), and other causes, with PaO_2/FiO_2 <250 mm Hg despite optimal oxygenation and ventilation, received placebo (n=193) or INOmax (n=192), 5 ppm, for 4 hours to 28 days or until weaned because of improvements in oxygenation. Despite acute improvements in oxygenation, there was no effect of INOmax on the primary endpoint of days alive and off ventilator support. These results were consistent with outcome data from a smaller dose ranging study of nitric oxide (1.25 to 80 ppm). INOmax is not indicated for use in ARDS.

INDICATIONS
INOmax, in conjunction with ventilatory support and other appropriate agents, is indicated for the treatment of term and near-term (>34 weeks) neonates with hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension, where it improves oxygenation and reduces the need for extracorporeal membrane oxygenation.

CONTRAINDICATIONS
INOmax should not be used in the treatment of neonates known to be dependent on right-to-left shunting of blood.

PRECAUTIONS
Rebound
Abrupt discontinuation of INOmax may lead to worsening oxygenation and increasing pulmonary artery pressure.

Methemoglobinemia
Methemoglobinemia increases with the dose of nitric oxide. In the clinical trials, maximum methemoglobin levels usually were reached approximately 8 hours after initiation of inhalation, although methemoglobin levels have peaked as late as 40 hours following initiation of INOmax therapy. In one study, 13 of 37 (35%) of neonates treated with INOmax 80 ppm had methemoglobin levels exceeding 7%. Following discontinuation or reduction of nitric oxide the methemoglobin levels returned to baseline over a period of hours.

Elevated NO_2 Levels
In one study, NO_2 levels were <0.5 ppm when neonates were treated with placebo, 5 ppm, and 20 ppm nitric oxide over the first 48 hours. The 80 ppm group had a mean peak NO_2 level of 2.6 ppm.

Drug Interactions
No formal drug-interaction studies have been performed, and a clinically significant interaction with other medications used in the treatment of hypoxic respiratory failure cannot be excluded based on the available data. INOmax has been administered with tolazoline, dopamine, dobutamine, steroids, surfactant, and high-frequency ventilation. Although there are no study data to evaluate the possibility, nitric oxide donor compounds, including sodium nitroprusside and nitroglycerin, may have an additive effect with INOmax on the risk of developing methemoglobinemia. An association between prilocaine and an increased risk of methemoglobinemia, particularly in infants, has specifically been described in a literature case report. This risk is present whether the drugs are administered as oral, parenteral, or topical formulations.

Carcinogenesis, Mutagenesis, Impairment of Fertility
No evidence of a carcinogenic effect was apparent, at inhalation exposures up to the recommended dose (20 ppm), in rats for 20 hr/day for up to two years. Higher exposures have not been investigated.

Nitric oxide has demonstrated genotoxicity in Salmonella (Ames Test), human lymphocytes, and after *in vivo* exposure in rats. There are no animal or human studies to evaluate nitric oxide for effects on fertility.

Pregnancy: Category C
Animal reproduction studies have not been conducted with INOmax. It is not known if INOmax can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. INOmax is not intended for adults.

Nursing Mothers
Nitric oxide is not indicated for use in the adult population, including nursing mothers. It is not known whether nitric oxide is excreted in human milk.

Pediatric Use
Nitric oxide for inhalation has been studied in a neonatal population (up to 14 days of age). No information about its effectiveness in other age populations is available.

ADVERSE REACTIONS
Controlled studies have included 325 patients on INOmax doses of 5 to 80 ppm and 251 patients on placebo. Total mortality in the pooled trials was 11% on placebo and 9% on INOmax, a result adequate to exclude INOmax mortality being more than 40% worse than placebo.

In both the NINOS and CINRGI studies, the duration of hospitalization was similar in INOmax and placebo-treated groups.

From all controlled studies, at least 6 months of follow-up is available for 278 patients who received INOmax and 212 patients who received placebo. Among these patients, there was no evidence of an adverse effect of treatment on the need for rehospitalization, special medical services, pulmonary disease, or neurological sequelae.

In the NINOS study, treatment groups were similar with respect to the incidence and severity of intracranial hemorrhage, Grade IV hemorrhage, periventricular leukomalacia, cerebral infarction, seizures requiring anticonvulsant therapy, pulmonary hemorrhage, or gastrointestinal hemorrhage.

The table below shows adverse events with an incidence of at least 5% on INOmax in the CINRGI study, and that were more common on INOmax than on placebo.

ADVERSE EVENTS IN THE CINRGI TRIAL

Adverse Event	Placebo (n=89)	Inhaled NO (n=97)
Hypotension	9 *(10%)*	13 *(13%)*
Withdrawal	9 *(10%)*	12 *(12%)*
Atelectasis	8 *(9%)*	9 *(9%)*
Hematuria	5 *(6%)*	8 *(8%)*
Hyperglycemia	6 *(7%)*	8 *(8%)*
Sepsis	2 *(2%)*	7 *(7%)*
Infection	3 *(3%)*	6 *(6%)*
Stridor	3 *(3%)*	5 *(5%)*
Cellulitis	0 *(0%)*	5 *(5%)*

OVERDOSAGE
Overdosage with INOmax will be manifest by elevations in methemoglobin and NO_2. Elevated NO_2 may cause acute lung injury. Elevations in methemoglobinemia reduce the oxygen delivery capacity of the circulation. In clinical studies, NO_2 levels >3 ppm or methemoglobin levels >7% were treated by reducing the dose of, or discontinuing, INOmax.

Methemoglobinemia that does not resolve after reduction or discontinuation of therapy can be treated with intravenous vitamin C, intravenous methylene blue, or blood transfusion, based upon the clinical situation.

POST-MARKETING EXPERIENCE
The following adverse events have been reported as part of the post-marketing surveillance. These events have not been reported above. Given the nature of spontaneously reported post-marketing surveillance data, it is impossible to determine the actual incidence of the events or definitively establish their causal relationship to the drug. The listing is alphabetical: dose errors associated with the delivery system; headaches associated with environmental exposure of INOmax in hospital staff; hypotension associated with acute withdrawal of the drug; hypoxemia associated with acute withdrawal of the drug; pulmonary edema in patients with CREST syndrome.

DOSAGE AND ADMINISTRATION
Dosage
The recommended dose of INOmax is 20 ppm. Treatment should be maintained up to 14 days or until the underlying oxygen desaturation has resolved and the neonate is ready to be weaned from INOmax therapy.

An initial dose of 20 ppm was used in the NINOS and CINRGI trials. In CINRGI, patients whose oxygenation improved with 20 ppm were dose-reduced to 5 ppm as tolerated at the end of 4 hours of treatment. In the NINOS trial, patients whose oxygenation failed to improve on 20 ppm could be increased to 80 ppm, but those patients did not then improve on the higher dose. As the risk of methemoglobinemia and elevated NO_2 levels increases significantly when INOmax is administered at doses >20 ppm, doses above this level ordinarily should not be used.

Administration
Additional therapies should be used to maximize oxygen delivery. In patients with collapsed alveoli, additional therapies might include surfactant and high-frequency oscillatory ventilation.

The safety and effectiveness of inhaled nitric oxide have been established in a population receiving other therapies for hypoxic respiratory failure, including vasodilators, intravenous fluids, bicarbonate therapy, and mechanical ventilation. Different dose regimens for nitric oxide were used in the clinical studies (see CLINICAL TRIALS).

INOmax should be administered with monitoring for PaO_2, methemoglobin, and NO_2.

The nitric oxide delivery systems used in the clinical trials provided operator-determined concentrations of nitric oxide in the breathing gas, and the concentration was constant throughout the respiratory cycle. INOmax must be delivered through a system with these characteristics and which does not cause generation of excessive inhaled nitrogen dioxide. The INOvent® system and other systems meeting these criteria were used in the clinical trials. In the ventilated neonate, precise monitoring of inspired nitric oxide and NO_2 should be instituted, using a properly calibrated analysis device with alarms. The system should be calibrated using a precisely defined calibration mixture of nitric oxide and nitrogen dioxide, such as INOcal®. Sample gas for analysis should be drawn before the Y-piece, proximal to the patient. Oxygen levels should also be measured.

In the event of a system failure or a wall-outlet power failure, a backup battery power supply and reserve nitric oxide delivery system should be available.

The INOmax dose should not be discontinued abruptly as it may result in an increase in pulmonary artery pressure (PAP) and/or worsening of blood oxygenation (PaO_2). Deterioration in oxygenation and elevation in PAP may also occur in children with no apparent response to INOmax. Discontinue/wean cautiously.

HOW SUPPLIED
INOmax (nitric oxide) is available in the following sizes:

Size D Portable aluminum cylinders containing 353 liters at STP of nitric oxide gas in 800 ppm concentration in nitrogen (delivered volume 344 liters) (NDC 64693-002-01)

Size D Portable aluminum cylinders containing 353 liters at STP of nitric oxide gas in 100 ppm concentration in nitrogen (delivered volume 344 liters) (NDC 64693-001-01)

Size 88 Aluminum cylinders containing 1963 liters at STP of nitric oxide gas in 800 ppm concentration in nitrogen (delivered volume 1918 liters) (NDC 64693-002-02)

Size 88 Aluminum cylinders containing 1963 liters at STP of nitric oxide gas in 100 ppm concentration in nitrogen (delivered volume 1918 liters) (NDC 64693-001-02)

Store at 25°C (77°F) with excursions permitted between 15–30°C (59–86°F) [see USP Controlled Room Temperature].

Occupational Exposure
The exposure limit set by the Occupational Safety and Health Administration (OSHA) for nitric oxide is 25 ppm, and for NO_2 the limit is 5 ppm.

CAUTION
Federal law prohibits dispensing without a prescription.

INO Therapeutics
6 Route 173 West
Clinton, NJ 08809
USA

SPC-0303 V:3.0

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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 09/12/2014

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

EXAMINER	
ARNOLD, ERNST V	
ART UNIT	PAPER NUMBER
1613	
MAIL DATE	DELIVERY MODE
09/12/2014	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 _____.

☐ 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 *8/7/14, 8/8/14, 8/13/14, 8/14/14, 8/15/14 and 8/25/14* .

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 statements (IDSs) submitted on 8/4/14, 8/5/14, 8/7/14, 8/14/14, 8/15/14 and 8/25/14 were filed before a first action on the merits. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statements are being considered by the examiner.

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.

Conclusion

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

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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
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ADDRESS

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

Inventor Information for 14/454373

Inventor Name	City	State/Country
BALDASSARRE, JAMES S.	DOYLESTOWN	PENNSYLVANIA

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

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Name/Print	Janis K. Fraser	Registration Number	34819

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	First Named Inventor	Baldassarre
	Art Unit	
	Examiner Name	
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	40	Office Action for AU 2010202422 dated 07/09/2010, 3 pages	☐
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Signature		Date (YYYY-MM-DD)	2014-08-04
Name/Print	Janis K. Fraser	Registration Number	34819

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

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	1	Fish & Richardson P.C., Supplemental Remarks in U.S. Serial No. 12/821,020, filed May 9, 2012 (22 pages)	☐
	2	U.S. Examiner Ernst V. Arnold, Interview Summary in U.S. Serial No. 12/821,020, mailed January 25, 2012 (4 pages)	☐
	3	Fish & Richardson P.C., Statement of the Substance of the Interview and Comments on Examiner's Interview Summary, in U.S. Serial No. 12/821,020, mailed January 25, 2012, filed February 27, 2012 (7 pages)	☐
	4	U.S. Examiner Ernst V. Arnold, Examiner's Answer in U.S. Serial No. 12/820,866, mailed November 2, 2011 (27 pages)	☐
	5	Fish & Richardson P.C., Express Abandonment in U.S. Serial No. 12/820,866 filed December 3, 2012 (1 page)	☐
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	8	Communication from Canadian Intellectual Property Office dated March 19, 2013, enclosing Protest from Robic regarding Canadian patent application no. 2,671,029 (42 pages)	☐
	9	Communication from Canadian Intellectual Property Office dated March 19, 2013, enclosing Protest from TORYS LLP regarding Canadian patent application no. 2,671,029 (36 pages)	☐
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	12	Himashree et al., "Nitric oxide and the respiratory system," Current Science, Vol. 85, No. 5, September 10, 2003, pages 607-614	☐
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	32	FROMM et al., "Congestive Heart Failure and Pulmonary Edema for the Emergency Physician," The Journal of Emergency Medicine, 13(1):71-87 (1995)	☐
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	42	Azeka et al., "Effects of Low Doses of Inhaled Nitric Oxide Combined with Oxygen for the Evaluation of Pulmonary Vascular Reactivity in Patients with Pulmonary Hypertension," Pediatric Cardiol., Vol. 23, pages 20-26 (2002)	☐
	43	Bland, "Pulmonary vascular dysfunction in preterm lambs with chronic lung disease," Am J Physical Lung Cell Mol. Physiol., Vol. 285: L76-L85 (2003)	☐
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	47		☐

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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)	2014-08-25
Name/Print	Janis K. Fraser	Registration Number	34819

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	Examiner	Art Unit
	ERNST V ARNOLD	1613

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	2	WO2005004884	WO		2005-01-20			☐
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	7	AU 2009202685 Office Action dated 06/17/10 (3 pages)	☐
	8	AU 2009202685 Office Action Response dated 07/29/2010, 19 pages	☐
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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)	2014-08-07
Name/Print	Janis K. Fraser	Registration Number	34819

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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
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	37	INO Thereapeutics, NCT00551642 at ClinicalTrials.gov (2007)	☐
	38	INOmax (nitric oxide) for inhalation 100 and 800 ppm (parts per million), drug label insert, 2007, 2 pages	☐
	39	Ivy et al., "Dipyridamole attenuates rebound pulmonary hypertension after inhaled nitric oxide withdrawal in postoperative congenital heart disease," J. Thorac. Cardiovasc. Surg.; Vol. 115, pages 875-882 (1998)	☐
	40	James et al., "Treatment of heart failure in children," Current Pediatrics, Vol. 15, 539-548 (2005)	☐
	41	JP 2009157623 Office Action dated 02/15/2011, 3 pages	☐
	42	JP 2009157623 Office Action dated 02/23/2010, 3 pages	☐
	43	JP 2009157623 Office Action dated 07/30/2010, 6 pages	☐
	44	JP 2009157623 Office Action response filed 06/18/2010, 37 pages (no translation)	☐

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Receipt date: 08/08/2014	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	
	Examiner Name	
	Attorney Docket Number	26047-0003011

	45	JP 2009157623 request for accelerated exam filed 01/15/2010 (60 pages)	☐
	46	JP 2009157623 response filed 11/30/2010, 58 pages	☐
	47	Kay et al., "Congestive heart failure in pediatric patients," From the Department of Pediatrics, Duke University Medical Center, by Mosby, Inc., 6 pages (2001)	☐
	48	Kazerooni et al., "Cardiopulmonary Imaging," Lippincott Williams & Wilkins, pages 234-235 (2 pages) (2004)	☐
	49	Kieler-Jensen et al., "Inhaled nitric oxide in the evaluation of heart transplant candidates with elevated pulmonary vascular resistance", J. Heart Lung Transplant, Vol. 13, pages 366-375 (1994)	☐
	50	Kinsella et al., "Inhaled nitric oxide in premature neonates with severe hypoxaemic respiratory faliure: a randomised controlled trial," The Lancet, Vol. 354, pages 1061-1065 (1999)	☐

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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)	2014-08-08
Name/Print	Janis K. Fraser	Registration Number	34819

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Doc Code: TRACK1.GRANT

Decision Granting Request for Prioritized Examination (Track I or After RCE)	Application No.: 14/454,373

1. THE REQUEST FILED 8/7//14 IS **GRANTED.**

The above-identified application has met the requirements for prioritized examination

A. ☒ for an original nonprovisional application (Track I).
B. ☐ for an application undergoing continued examination (RCE).

2. **The above-identified application will undergo prioritized examination.** The application will be accorded special status throughout its entire course of prosecution until one of the following occurs:

A. filing a **petition for extension of time** to extend the time period for filing a reply;
B. filing an **amendment to amend the application to contain more than four independent claims, more than thirty total claims**, or a multiple dependent claim;
C. filing a **request for continued examination**;
D. filing a notice of appeal;
E. filing a request for suspension of action;
F. mailing of a notice of allowance;
G. mailing of a final Office action;
H. completion of examination as defined in 37 CFR 41.102; or
I. abandonment of the application.

Telephone inquiries with regard to this decision should be directed to Terri Johnson at 571-272-2991

/Terri Johnson/ Paralegal Specialist

[*Signature*] (Title)

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

PTO/SB/08a (01-10)
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	Filing Date	2014-08-07
	First Named Inventor	Baldassarre
	Art Unit	
	Examiner Name	
	Attorney Docket Number	26047-0003011

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	1	Fish & Richardson P.C., Supplemental Remarks in U.S. Serial No. 12/821,020, filed May 9, 2012 (22 pages)	☐
	2	U.S. Examiner Ernst V. Arnold, Interview Summary in U.S. Serial No. 12/821,020, mailed January 25, 2012 (4 pages)	☐
	3	Fish & Richardson P.C., Statement of the Substance of the Interview and Comments on Examiner's Interview Summary, in U.S. Serial No. 12/821,020, mailed January 25, 2012, filed February 27, 2012 (7 pages)	☐
	4	U.S. Examiner Ernst V. Arnold, Examiner's Answer in U.S. Serial No. 12/820,866, mailed November 2, 2011 (27 pages)	☐
	5	Fish & Richardson P.C., Express Abandonment in U.S. Serial No. 12/820,866 filed December 3, 2012 (1 page)	☐
	6	U.S. Examiner Ernst V. Arnold, Notice of Abandonment in U.S. Serial No. 12/820,866, mailed December 20, 2012 (2 pages)	☐
	7	Autorisation De Mise Sur Le Marche for VasoKINOX 450 ppm mole/mole issued by the Federal Agency for Drug and Medical Product (AFMPS or FAMPH) (BE 320336) dated 14/07/2008 (37 pages) (including English translation)	☐
	8	Communication from Canadian Intellectual Property Office dated March 19, 2013, enclosing Protest from Robic regarding Canadian patent application no. 2,671,029 (42 pages)	☐
	9	Communication from Canadian Intellectual Property Office dated March 19, 2013, enclosing Protest from TORYS LLP regarding Canadian patent application no. 2,671,029 (36 pages)	☐
	10	Hess, "Heliox and Inhaled Nitric Oxide," Mechanical Ventilation, Chapter 28 (2001), pages 454-480	☐
	11	Free Merriam-Webster Dictionary, definition of "supplying", pages 1-4, downloaded April 22, 2013	☐

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	12	Himashree et al., "Nitric oxide and the respiratory system," Current Science, Vol. 85, No. 5, September 10, 2003, pages 607-614	☐
	13	Kazerooni, Cardiopulmonary Imaging 2004, Lippincott Williams & Wilkins, "Left Ventricular Function", pages 234 and 236 (in part)	☐
	14	Leo, "Competency and the Capacity to Make Treatment Decisions: A Primer for Primary Care Physicians," Primary Care Companion J. Clin. Psychiatry, Vol 1, No. 5, October 1999, pages 131-141	☐
	15	Loh et al., "Cardiovascular Effects of Inhaled Nitric Oxide in Patients With Left Ventricular Dysfunction," Circulation, Vol. 90, pages 2780-2785 (1994)	☐
	16	McLaughlin et al., "Pulmonary Arterial Hypertension," Circulation, Vol. 114, pages 1417-1431 (2006)	☐
	17	Canadian Intellectual Property Office, Requisition by the examiner in CA Appl. 2,671,029; Apr. 25, 2013; 24 pp.	☐
	18	Stewart et al.; Hypoxic Respiratory Failure: Diagnosis and Treatment, 36th Annual Pacific Northwest Regional Respiratory Care Conference and Scientific Assembly; Apr. 26, 2009; pp. 1-71	☐
	19	Preston et al.; Pulmonary Edema Caused by Inhaled Nitric Oxide therapy in Two Patients with Pulmonary Hypertension Associated with the CREST Syndrome; Chest 121:656-659 (2002)	☐
	20	Description of the clinical trial NCT00626028 published online on the website http://clinicaltrials.gov/archive/NCT00626028; Feb. 28, 2008.	☐
	21	Bernasconi et al.; Inhaled Nitric Oxide Applications in Pediatric Practice, Images in Pediatric Cardiology, Vol. 4(1), Jan-Mar 2002; pages 4-29.	☐
	22	Torys LLP, Letter to Canadian Commissioner of Patents relating to CA 2,671,029; Aug. 9, 2013;	☐

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	23	McMullan et al., Alterations in Endogenous Nitric Oxide Production After Cardiopulmonary Bypass in Lambs with Normal and Increased Pulmonary Blood Flow; Circulation 102 [suppl III]:III-172-III-178 (2000)	☐
	24	Clutton-Brock, Two Cases of Poisoning by Contamination of Nitrous Oxide with Higher Oxides of Nitrogen During Anaesthesia; Brit. J. Anaesth. 39:388-392 (1967)	☐
	25	Shiel, Morbid Anatomical Changes in the Lungs of Dogs after Inhalation of Higher Oxides of Nitrogen During Anaesthesia; Brit. J. Anaesth. 39:413-424 (1967)	☐
	26	Federal Agency for Medicines and Health Products (European Union), Public Assessment Report, Decentralised Procedure, VasoKINOX 450 ppm mole/mole, inhalation gas, cylinder, Nitric Oxide; Jul. 14, 2008; 34 pages	☐
	27	Weinberger et al., Pulmonary Hypertension, Chapter 14 of Principles of Pulmonary Medicine, Elsevier Saunders, 2014; pp 189-200	☐
	28	Hayward et al., Inhaled nitric oxide in cardiology practice; Cardiovascular Research 43:628-638 (1999)	☐
	29	THE NEONATAL INHALED NITRIC OXIDE STUDY GROUP, "Inhaled Nitric Oxide in Full-Term and Nearly Full-Term Infants with Hypoxic Respiratory Failure," New England Journal of Medicine, 336(9):597-604 (1997)	☐
	30	BURKHOFF et al., "Why does pulmonary venous pressure rise after onset of LV dysfunction: a theoretical analysis," Am. J. Physiol., 34:H1819-H1828 (1993)	☐
	31	Prior art notice issued in CA267102 on August 9, 2013 (51 pages)	☐
	32	FROMM et al., "Congestive Heart Failure and Pulmonary Edema for the Emergency Physician," The Journal of Emergency Medicine, 13(1):71-87 (1995)	☐
	33	MOURANI et al., "Left Ventricular Diastolic Dysfunction in Bronchopulmonary Dysplasia," J. of Pediatrics, 152:291-293 (2008)	☐

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	34	Rosales et al., "Adverse Hemodynamic Effects Observed with Inhaled Nitric Oxide After Surgical Repair of Total Anomalous Pulmonary Venous Return," Pediatric Cardiology, 20:224-226 (1999)	☐
	35	PRAXAIR, INC. Protest filed against CA2,671,029 on June 2, 2014 (38 pages)	☐
	36	Prior art notice issued in CA267102 on August 9, 2013 (51 pages)	☐
	37	Stewart et al.; Hypoxic Respiratory Failure: Diagnosis and Treatment, 36th Annual Pacific Northwest Regional Respiratory Care Conference and Scientific Assembly; Apr. 26, 2009; pp. 1-71	☐
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	39	Loh et al., "Cardiovascular Effects of Inhaled Nitric Oxide in Patients with Left Ventricular Dysfunction," Circulation, Vol. 90, pages 2780-2785 (1994)	☐
	40	Martinez et al., "Dermatological Cryosurgery in Primary Care with Dimethyl Ether Propane Spray in Comparison with Liquid Nitrogen," Atencion Primaria, Vol. 18, No. 5, pages 211 and 216 (1996)	☐
	41	Adatia et al., "Inhaled Nitric Oxide and Hemodynamic Evaluation of Patients With Pulmonary Hypertension Before Transplantation," Journal of the American College of Cardiology, Elsevier, New York, NY, Vol. 25, No. 7, page 1663, June 1, 1995	☐
	42	Azeka et al., "Effects of Low Doses of Inhaled Nitric Oxide Combined with Oxygen for the Evaluation of Pulmonary Vascular Reactivity in Patients with Pulmonary Hypertension," Pediatric Cardiol., Vol. 23, pages 20-26 (2002)	☐
	43	Bland, "Pulmonary vascular dysfunction in preterm lambs with chronic lung disease," Am J Physical Lung Cell Mol. Physiol., Vol. 285: L76-L85 (2003)	☐
	44	Field, "Neonatal Ventilation With Inhaled Nitric Oxide Versus Ventilatory Support Without Inhaled Nitric Oxide for Preterm Infants With Severe Respiratory Failure: The INNOVO Multicentre Randomised Controlled Trial (ISRCTN 17821339)," Pediatrics Journal, Vol. 115, pages 926-936 (2005) DOI: 10.1542/peds.2004-1209	☐

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	45	Green, "Patent Ductus Arteriosus Demonstrating Shunting of Blood," Figure from presentation given 1/10/2011	☐
	46	INO Therapeutics, NCT00551642 at ClinicalTrials.gov (2007)	☐
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Signature	/Janis K. Fraser/	Date (YYYY-MM-DD)	2014-08-25
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Electronic Acknowledgement Receipt

EFS ID:	19959297
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:	25-AUG-2014
Filing Date:	07-AUG-2014
Time Stamp:	17:49:38
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	Transmittal Letter	IDS.pdf	63196 83ec4bfc9ad5c29896dcc3f123e328a5bd0da96a	no	1

Warnings:	
Information:	

2	Information Disclosure Statement (IDS) Form (SB08)	SB08.pdf	615487 f8d2fe6e1c1b631fc61ce5f786fb2ccaa41be7a9	no	8
Warnings:					
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3	Non Patent Literature	Prior.pdf	2663485 43ce84564d9d064e826444ac45e8c812cb17db9c	no	38
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Information:					
4	Non Patent Literature	Rosales.pdf	3360703 e17690f3f5539e78723d6ec621c22a54e25b2b6f	no	51
Warnings:					
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5	Non Patent Literature	Stew.pdf	2770914 0a7f1b9dbad81f15cbc16ad6e749987c6cfd389a	no	71
Warnings:					
Information:					
			Total Files Size (in bytes):	9473785	

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<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.

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	:	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

SIXTH INFORMATION DISCLOSURE STATEMENT

Please consider the references listed on the enclosed PTO-SB-08 Form. Under 35 USC §120, this application relies on the earlier filing dates of application serial numbers 12/494,598, filed on June 30, 2009; 12/820,866, filed on June 22, 2010; 12/821,041, filed on June 22, 2010; 13/651,660, filed on October 15, 2012; 13/683,417, filed on November 21, 2012; 13/683,444, filed on November 21, 2012; and 14/451,057, filed on August 4, 2014. References 1-34 and 38-46 were submitted to and/or cited by the Office in one or more of the prior applications and therefore are not provided in this application. Copies of references 35-37 are attached. References 38-46 were cited in PTO-SB-08 Forms previously submitted in the present application and are being re-cited here to correct typographical errors present in the prior submissions.

This statement is being filed within three months of the filing date of the application. Apply any necessary charges or credits to Deposit Account 06-1050, referencing the above attorney docket number.

Respectfully submitted,

Date: August 25, 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

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number: 14/454,373

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY FEE($)
BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	70		N/A	
SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A	300		N/A	
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	360		N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	30 minus 20 =	* 10	x 40 =	400	OR		
INDEPENDENT CLAIMS (37 CFR 1.16(h))	4 minus 3 =	* 1	x 210 =	210			
APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).			0.00			
MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))				0.00			
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL	1340		TOTAL	

APPLICATION AS AMENDED - PART II

AMENDMENT A

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY ADDITIONAL FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE($)
Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
Application Size Fee (37 CFR 1.16(s))									
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
					TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

AMENDMENT B

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY ADDITIONAL FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE($)
Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
Application Size Fee (37 CFR 1.16(s))									
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
					TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".

*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".

The "Highest Number Previously Paid For" (Total or Independent) is the highest found in the appropriate box in column 1.

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APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
14/454,373	08/07/2014	1616	1340	26047-0003011	30	4

CONFIRMATION NO. 3860

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

FILING RECEIPT

OC000000070224328

Date Mailed: 08/18/2014

Receipt is acknowledged of this non-provisional patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please submit a written request for a Filing Receipt Correction. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections**

Inventor(s)

James S. Baldassarre, Doylestown, PA;

Applicant(s)

INO Therapeutics LLC, Hampton, NJ

Assignment For Published Patent Application

INO THERAPEUTICS LLC, Hampton, NJ

Power of Attorney: The patent practitioners associated with Customer Number 94169

Domestic Priority data as claimed by applicant

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

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 for which priority is claimed (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see http://www.uspto.gov for more information.) - None.
Foreign application information must be provided in an Application Data Sheet in order to constitute a claim to foreign priority. See 37 CFR 1.55 and 1.76.

If Required, Foreign Filing License Granted: 08/15/2014

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 14/454,373**

Projected Publication Date: 11/27/2014

Non-Publication Request: No

Early Publication Request: No
**** SMALL ENTITY ****
Title

Methods for improving the safety of treating pediatric patients who are candidates for inhaled nitric oxide treatment

Preliminary Class

424

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications: No

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

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For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, http://www.stopfakes.gov. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4258).

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Title 37, Code of Federal Regulations, 5.11 & 5.15

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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	
	Examiner Name	
	Attorney Docket Number	26047-0003011

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
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	Examiner Name	
	Attorney Docket Number	26047-0003011

	1	U.S. Examiner Ernst V. Arnold, Office Action in U.S. Serial No. 12/494,598, mailed August 13, 2010 (26 pages)	☐
	2	U.S. Examiner Ernst V. Arnold, Notice of Abandonment in U.S. Serial No. 12/494,598, mailed September 10, 2010 (2 pages)	☐
	3	U.S. Examiner Ernst V. Arnold, Office Action in U.S. Serial No. 12/820,866, mailed September 23, 2010 (26 pages)	☐
	4	Lee & Hayes, Reply in U.S. Serial No. 12/820,866, filed October 1, 2010 (22 pages)	☐
	5	U.S. Examiner Ernst V. Arnold, Office Action in U.S. Serial No. 12/820,866, mailed November 2, 2010 (25 pages)	☐
	6	Lee & Hayes, Reply in U.S. Serial No. 12/820,866, filed January 14, 2011 (12 pages)	☐
	7	U.S. Examiner Ernst V. Arnold, Advisory Action in U.S. Serial No. 12/820,866, mailed February 23, 2011 (2 pages)	☐
	8	Lee & Hayes, Reply After Final in U.S. Serial No. 12/820,866, filed March 1, 2011 (9 pages)	☐
	9	Lee & Hayes, Reply After Final in U.S. Serial No. 12/820,866, filed March 3, 2011 (5 pages)	☐
	10	U.S. Examiner Ernst V. Arnold, Advisory Action in U.S. Serial No. 12/820,866, mailed March 25, 2011 (3 pages)	☐
	11	Lee & Hayes, Reply After Final in U.S. Serial No. 12/820,866, filed May 2, 2011 (9 pages)	☐

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	Attorney Docket Number	26047-0003011

	12	U.S. Examiner Ernst V. Arnold, Office Action in U.S. Serial No. 12/820,866, mailed June 8, 2011 (32 pages)	☐
	13	U.S. Examiner Ernst V. Arnold, Office Action in U.S. Serial No. 12/820,866, August 24, 2011 (23 pages)	☐
	14	Fish & Richardson, P.C., Reply Brief in U.S. Serial No. 12/820,866, filed December 16, 2011 (21 pages)	☐
	15	Fish & Richardson, P.C., Supplement to Reply Brief in U.S. Serial No. 12/820,866, filed January 3, 2012 (3 pages)	☐
	16	U.S. Examiner Ernst V. Arnold, Office Action in U.S. Serial No. 12/820,980, mailed August 17, 2010 (33 pages)	☐
	17	Lee & Hayes, Reply Amendment in U.S. Serial No. 12/820,980, filed September 17, 2010 (25 pages)	☐
	18	U.S. Examiner Ernst V. Arnold, Office Action in U.S. Serial No. 12/820,980, mailed October 28, 2010 (23 pages)	☐
	19	U.S. Examiner Ernst V. Arnold, Supplemental Office Action in U.S. Serial No. 12/820,980, mailed November 2, 2010 (4 pages)	☐
	20	Lee & Hayes, Reply after Final in U.S. Serial No. 12/820,980, filed November 12, 2010 (53 pages)	☐
	21	U.S. Examiner Ernst V. Arnold, Advisory Action in U.S. Serial No. 12/820,980, mailed November 29, 2010 (3 pages)	☐
	22	Lee & Hayes, Reply after Final in U.S. Serial No. 12/820,980, filed May 2, 2011 (23 pages)	☐

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	Attorney Docket Number	26047-0003011

	23	U.S. Examiner Ernst V. Arnold, Office Action in U.S. Serial No. 12/820,980, mailed June 10, 2011 (29 pages)	☐
	24	Lee & Hayes, Amendment in Reply to Office Action in U.S. Serial No. 12/820,980, filed July 11, 2011 (115 pages)	☐
	25	U.S. Examiner Ernst V. Arnold, Office Action in U.S. Serial No. 12/820,980, mailed September 9, 2011 (25 pages)	☐
	26	U.S. Examiner Ernst V. Arnold, Notice of Abandonment in U.S. Serial No. 12/820,980, mailed April 11, 2012 (2 pages)	☐
	27	U.S. Examiner Ernst V. Arnold, Office Action in U.S. Serial No. 12/821,020, mailed August 13, 2010 (24 pages)	☐
	28	Lee & Hayes, Response to Office Action in U.S. Serial No. 12/821,020, filed February 14, 2011 (18 pages)	☐
	29	Lee & Hayes, Supplemental Reply Amendment in U.S. Serial No. 12/821,020, filed April 12, 2011 (9 pages)	☐
	30	U.S. Examiner Ernst V. Arnold, Office Action in U.S. Serial No. 12/821,020, mailed June 27, 2011 (28 pages)	☐
	31	Fish & Richardson, P.C., Amendment in Reply to Office Action in U.S. Serial No. 12/821,020, filed December 27, 2011 (31 pages)	☐
	32	U.S. Examiner Ernst V. Arnold, Office Action in U.S. Serial No. 12/821,020, mailed January 31, 2012 (23 pages)	☐
	33	U.S. Examiner Ernst V. Arnold, Interview Summary in U.S. Serial No. 12/821,020, mailed April 17, 2012 (4 pages)	☐

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	First Named Inventor	Baldassarre
	Art Unit	
	Examiner Name	
	Attorney Docket Number	26047-0003011

	34	Fish & Richardson, P.C., Statement of Substance of Interview and Comments on Examiner's Interview Summary, in U.S. Serial No. 12/821,020, filed April 23, 2012 (8 pages)	☐
	35	Fish & Richardson, P.C., Supplemental Amendment in U.S. Serial No. 12/821,020, filed April 30, 2012 (10 pages)	☐
	36	U.S. Examiner Ernst V. Arnold, Office Action in U.S. Serial No. 12/821,020, mailed June 15, 2012 (56 pages)	☐
	37	Fish & Richardson, P.C., Amendment in U.S. Serial No. 12/821,020, filed August 15, 2012 (15 pages)	☐
	38	U.S. Examiner Ernst V. Arnold, Office Action in U.S. Serial No. 12/821,041, mailed August 17, 2010 (32 pages)	☐
	39	Lee & Hayes, Reply in U.S. Serial No. 12/821,041, filed February 14, 2011 (28 pages)	☐
	40	Lee & Hayes, Supplemental Reply in U.S. Serial No. 12/821,041, filed April 13, 2011 (9 pages)	☐
	41	U.S. Examiner Ernst V. Arnold, Office Action in U.S. Serial No. 12/821,041, mailed June 27, 2011 (35 pages)	☐
	42	Fish & Richardson, P.C., Amendment in Reply to Office Action in U.S. Serial No. 12/821,041, filed January 6, 2012 (155 pages)	☐
	43	U.S. Examiner Ernst V. Arnold, Office Action in U.S. Serial No. 12/821,041, mailed February 10, 2012 (36 pages)	☐
	44	Fish & Richardson, P.C., Supplemental Amendment and Remarks in U.S. Serial No. 12/821,041, filed May 11, 2012 (32 pages)	☐

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
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	Examiner Name	
	Attorney Docket Number	26047-0003011

	45	U.S. Examiner Ernst V. Arnold, Office Action in U.S. Serial No. 12/821,041, mailed June 19, 2012 (61 pages)	☐
	46	Fish & Richardson, P.C., Amendment in Reply to Office Action in U.S. Serial No. 12/821,041, filed August 15, 2012 (17 pages)	☐
	47	Lee & Hayes, Amendment in Reply to Office Action in U.S. Serial No. 12/820,866, filed July 8, 2011 (23 pages)	☐
	48	Fish & Richardson, Brief on Appeal in U.S. Serial No. 12/820,866, filed October 4, 2011 (211 pages)	☐
	49	U.S. Examiner Ernst V. Arnold, Interview Summary in U.S. Serial No. 12/821,020, mailed January 25, 2012 (4 pages)	☐

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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	
	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).

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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.

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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)	2014-08-15
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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Electronic Acknowledgement Receipt

EFS ID:	19882025
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:	15-AUG-2014
Filing Date:	07-AUG-2014
Time Stamp:	17:24:24
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	Transmittal Letter	IDS.pdf	63007 691d3282f02e40c5ff3abd0dc2e8bc5f6b55c30d	no	1
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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	:	METHODS FOR IMPROVING THE SAFETY OF TREATING PEDIATRIC PATIENTS WHO ARE CANDIDATES FOR INHALED NITRIC OXIDE TREATMENT		

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Commissioner for Patents
P.O. Box 1450
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FIFTH INFORMATION DISCLOSURE STATEMENT

Please consider the references listed on the enclosed PTO-SB-08 Form. Under 35 USC §120, this application relies on the earlier filing dates of application serial numbers 12/494,598, filed on June 30, 2009; 12/820,866, filed on June 22, 2010; 12/821,041, filed on June 22, 2010; 13/651,660, filed on October 15, 2012; 13/683,417, filed on November 21, 2012; 13/683,444, filed on November 21, 2012; and 14/451,057, filed on August 4, 2014. The cited references were submitted to and/or cited by the Office in one or more of the prior applications and therefore are not provided in this application.

This statement is being filed within three months of the filing date of the application. Apply any necessary charges or credits to Deposit Account 06-1050, referencing the above attorney docket number.

Respectfully submitted,

Date: August 15, 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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	Filing Date	2014-08-07
	First Named Inventor	Baldassarre
	Art Unit	
	Examiner Name	
	Attorney Docket Number	26047-0003011

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	1	Ratnasamy et al., "Associations between neurohormonal and inflammatory activation and heart failure in children," American Heart Journal, pages 527-533 (2008)	☐
	2	Response filed 08/18/2010 to EP Search Report dated 05/10/10 for EP09251949	☐
	3	Ricciardi et al., "Inhaled Nitric Oxide in Primary Pulmonary Hypertension: A Safe and Effective Agent for Predicting Response to Nifedipine," Journal of the American College of Cardiology (JACC,) Vol. 32, No. 4, pages 1068-1073 (1998)	☐
	4	Roberts, "Inhaled Nitric Oxide and Persistent Pulmonary Hypertension of the Newborn," The New England Journal of Medicine, Vol. 336, No 9, pages 605-610 (1997)	☐
	5	Roberts, "Nitric Oxide and the Lung," Marcel Dekker, Inc., New York, NY, pages 333-363 (1997)	☐
	6	Rosales et al., "Hemodynamic Effects Observed with Inhaled Nitric Oxide After Surgical Repair of Total Anamolous Pulmonary Venous Return," Pediatric Cardiology, Vol. 20, pages 224-226 (1999)	☐
	7	Rosenberg, "Inhaled nitric oxide in the premature infant with severe hypoxemic respiratory failure: A time for caution," The Journal of Pediatrics, Volume 133, Issue 6 , pages 720-722 (1998)	☐
	8	Sadiq et al., "Inhaled Nitric Oxide in the Treatment of Moderate Persistent Pulmonary Hypertension of the Newborn: A Randomized Controlled, Multicenter Trial," Journal of Perinatology, Vol. 23, pages 98-103 (2003)	☐
	9	Search Report from EP 09251949 dated 05/10/10	☐
	10	Sehgal et al., "Experience with Inhaled Nitric Oxide Therapy in Hypoxic Respiratory Failure of the Newborn," Indian J. Chest Dis. Allied. Sci., Vol. 47, pages 245-249 (2005)	☐
	11	Semigran et al., "Hemodynamic Effects of Inhaled Nitric Oxide in Heart Failure," Journal of American College of Cardiology (JACC), Vol. 24, No. 4, pages 982-988 (1994)	☐

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	12	Shapiro et al., "Diagnostic Dilemmas: Diastolic Heart Failure Causing Pulmonary Hypertension and Pulmonary Hypertension Causing Diastolic Dysfunction," Advances in Pulmonary Hypertension, Vol. 5(1), pages 13-20 (2006) http://www.phaonlineuniv.org/sites/default/files/spr_2006.pdf	☐
	13	"Sibutramine-metformin Combination vs. Sibutramine and Metformin Monotherapy in Obese Patients, page 3, ClinicalTrials.gov, <<http://clinicaltrials.gov/ct2/showNCT00941382>> Sponsored by Laboratorios Silanes S.A. de C.V. and Jorge González Canudas, July 15, 2009	☐
	14	Singh et al., "Nitric Oxide, the biological mediator of the decade: fact or fiction?," Eur. Respir. J. , Vol. 10, pages 699-707 (1997)	☐
	15	Smyth, "Inhaled nitric oxide treatment for preterm infants with hypoxic respiratory failure," Thorax, Vol. 55 (Suppl 1), pages S51-S55 (2000)	☐
	16	Somarriba et al., "Exercise rehabilitation in pediatric cardiomyopathy," Progress in Pediatric Cardiology, Vol. 25, pages 91-102 (2008)	☐
	17	Soto et al., "Cardiopulmonary Hemodynamics in Pulmonary Hypertension: Pressure Tracings, Waveforms, and More," Advances in Pulmonary Hypertension Winter, Vol. 7(4), pages 386-393 (2008)	☐
	18	Steinhorn et al., "Inhaled nitric oxide enhances oxygenation but not survival in infants with alveolar capillary dysplasia," The Journal of Pediatrics, Vol. 130(3), pages 417-422 (1997)	☐
	19	Steinhorn, "Persistent Pulmonary Hypertension in the Newborn and Infant," Vol. 1(2), pages 287-299 (1987)	☐
	20	Steinhorn, "Pulmonary Hypertension, Persistent-Newborn," Updated April 19, 2007, http://emedicine.medscape.com/article/898437-overview	☐
	21	Steudel et al., "Inhaled nitric oxide," Anesthesiology, Vol. 91, pages 1090-1121 (1999)	☐
	22	Strauss et al., "Pediatric Cardiomyopathy - A Long Way to Go," The New England Journal of Medicine, Vol. 348, no. 17, pages1703-1705 (2003)	☐

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	23	Toshniwal, et al., "Study of Comparative Effects of Oral Clonidine vs. Oral Diazepam Pre-Medication on the Extent and Duration of Sensory Blockade in Patients Undergoing Vaginal Hysterectomy Under Spinal Anaesthesia", Internet Journal of Anesthesiology (2009) <<http://www.britannica.com/bps/additionalcontent/18/41575551/Study-of-Comparative-Effects-Oral-Clonidine-vs-Oral-Diazepam-Pre-Medication-on-the-Extent-and-Duration-of-Sensory-Blockade-in-Patients-Undergoing-Vaginal-Hysterectomy-Under-Spinal-Anaesthesia>>	☐
	24	The American Illustrated Medical Dictionary (Dorland, 7th ed., page 113) (1914)	☐
	25	The Effects of Nitric Oxide for Inhalation on the Development of Chronic Lung Disease in Pre-Term Infants, from ClinicalTrials.gov archive, NCT00551642, 10/30/2007, 3 pages	☐
	26	The Encarta Webster's Dictionary of the English Language (2004) is the second edition of the Encarta World Dictionary, published 1999, <<http://encarta.msn.com/encnet/features/dictionary/dictionaryhome.aspx>>; used to look up the definitions of "precaution" and "exclusion"	☐
	27	The Neonatal Inhaled Nitric Oxide Study Group, The New England Journal of Medicine, Vol. 336(9), pages 597-604 (1997)	☐
	28	The NIH, Critical Care Therapy and Respiratory Care Section, Nitric Oxide Therapy, 13 pages (May 2000)	☐
	29	Towbin et al., "Incidence, Causes, and Outcomes of Dilated Cardiomyopathy in Children," JAMA, Vol. 296, No. 15, pages 1867-1876 (2006)	☐
	30	Translated copy of the Japanese Office Action mailed February 15, 2011 for Japanese Patent Application No.2009-157623, a counterpart foreign application for US Patent Application No. 12/494,598	☐
	31	Troncy et al. "Inhaled nitric oxide: clinical applications, indications, and toxicology," Can. J. Anaesth, Vol. 44 (9), pages 972-988 (1997)	☐
	32	UCI General Clinical Research Center, Federal Regulations 21 CFR Part 312, <<http://www.gcrc.uci.edu/rsa/aer.cfm>>, retrieved 9/13/2010, 2 pages	☐
	33	University of Alabama, NCT00732537 at Clinicaltrials.gov (2008)	☐

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	34	"Use of Inhaled Nitric Oxide," American Academy of Pediatrics - Committee on Fetus and Newborn, Pediatrics Vol. 106, No. 2, pages 344-345 (2000)	☐
	35	UTMB Respiratory Care Services, "Delivery of Inhaled Nitric Oxide Therapy through an Adult or Pediatric Nasal Cannula," 4 pages, (2003)	☐
	36	van Dalen, "Treatment for Asymptomatic Anthracycline-Induced Cardiac Dysfunction in Childhood Cancer Survivors: The Need for Evidence," Journal of Clinical Oncology, Vol 21, No 17, pages 3375-3379 (2003)	☐
	37	Watson et al., "Clinical and Economic Effects of iNO in Premature Newborns With Respiratory Failure at 1 Year", Pediatrics, Vol. 124, pages 1333-1343 (2009)	☐
	38	Weinberger et al., "The Toxicology of Inhaled Nitric Oxide," Toxicological Sciences, Vol. 59, pages 5-16 (2001)	☐
	39	Weinberger et al., "Nitric Oxide in the lung: therapeutic and cellular mechanisms of action", Pharmacology & Therapeutics, Vol. 84, pages 401-411 (1999)	☐
	40	Wessel et al., "Improved Oxygenation in a Randomized Trial of Inhaled Nitric Oxide for Persistent Pulmonary Hypertension of the Newborn," Pediatrics, Vol. 100, No. 5, page E7 (1997)	☐
	41	Wessel et al., "Managing low cardiac output syndrome after congenital heart surgery," Crit. Care Med., Vol. 29(10) pages S220-S230 (2001)	☐
	42	Wheeler et al., "The Central Nervous System in Pediatric Critical Illness and Injury," Pediatric Critical Care Medicine, Springer, page 278 (2007)	☐
	43	Wilkinson et al., "Epidemiological and outcomes research in children with pediatric cardiomyopathy; discussions from the international workshop on primary and idiopathic cardiomyopathies in children," Progress in Pediatric Cardiology, Vol. 25, pages 23-25 (2008)	☐
	44	Yoshida, "Well-illustrated Diagnostics and Treatment of Heart Failure," Circulation, Vol. 2, No. 4, pages 23-28 (2007)	☐

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	45	Ameduri et al., Heart Failure in Children, MED-Continuing Medical Education, University of Minnesota. 2009 July 29, (cited 2010 Nov 12); available from URL: ttp://www.cme.umn.edu/prod/groups/med/@pub/@med/@cme/documents/content/med_content_124593.pdf	☐
	46	Konduri, "Early inhaled nitric oxide therapy for term and near-term newborn infants with hypoxic respiratory failure: neurodevelopmental follow-up," J. Pediatr. Vol. 150(3), pages 235-240, 240.e.1 (2007)	☐
	47	Barrington et al., "Inhaled nitric oxide for respiratory failure in preterm infants (review)," The Cochrane Collaboration, Wiley Publishers, 3 pages (2009)	☐
	48	Barst, "Vasodilator Testing with Nitric Oxide and/or Oxygen in Pediatric Pulmonary Hypertension," Pediatr. Cardiol., Vol. 31, pages 598-606 (2010)	☐
	49	Macrae, "Drug therapy in persistent pulmonary hypertension of the newborn," Semin. Neonatal, Vol. 2, pages 49-58 (1997)	☐
	50	Miller et al., "Guidelines for the safe administration of inhaled nitric oxide," Archives of Disease in Childhood, Vol. 10, pages F47-F49 (1994)	☐

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Signature	/Janis K. Fraser/	Date (YYYY-MM-DD)	2014-08-14
Name/Print	Janis K. Fraser	Registration Number	34819

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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.

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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.

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EFS ID:	19871185
Application Number:	14454373
International Application Number:	
Confirmation Number:	3860
Title of Invention:	Methods of Treating Term and Near-Term Neonates Having Hypoxic Respiratory Failure Associated with Clinical or Echocardiographic Evidence of Pulmonary Hypertension
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-AUG-2014
Filing Date:	
Time Stamp:	17:16:15
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	Transmittal Letter	IDS.pdf	63010 3d22ecae787d8a1a25740a877a3eebdfc13abeb8	no	1
Warnings:					
Information:					

2	Information Disclosure Statement (IDS) Form (SB08)	SB08.pdf	616030 8407dcb6158fcf48aaafb7f464c7288401257e3b	no	8

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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.

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	:	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

FOURTH INFORMATION DISCLOSURE STATEMENT

Please consider the references listed on the enclosed PTO-SB-08 Form. Under 35 USC §120, this application relies on the earlier filing dates of application serial numbers 12/494,598, filed on June 30, 2009; 12/820,866, filed on June 22, 2010; 12/821,041, filed on June 22, 2010; 13/651,660, filed on October 15, 2012; 13/683,417, filed on November 21, 2012; 13/683,444, filed on November 21, 2012; and 14/451,057, filed on August 4, 2014. The cited references were submitted to and/or cited by the Office in one or more of the prior applications and therefore are not provided in this application.

This statement is being filed within three months of the filing date of the application. Apply any necessary charges or credits to Deposit Account 06-1050, referencing the above attorney docket number.

Respectfully submitted,

Date: August 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: (877) 769-7945

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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.

Amendments to the Specification:

Replace the title on page 1 with the following new title:

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

Amendments to the Abstract:

Delete the previous abstract at page 29 and add the following new abstract:

Disclosed are methods of reducing the risk that a medical treatment comprising inhalation of nitric oxide gas will induce an increase in pulmonary capillary wedge pressure in pediatric patients, leading to pulmonary edema. The methods include avoiding or discontinuing administration of inhaled nitric oxide to a pediatric patient determined to have pre-existing left ventricular dysfunction but who otherwise is a candidate for inhaled nitric oxide treatment (e.g., for pulmonary hypertension), and administering inhaled nitric oxide to pediatric patients who are candidates for such treatment and who are determined not to have pre-existing left ventricular dysfunction.

Amendments to the Claims:

This listing of claims replaces all prior versions and listings of claims in the application:

Listing of Claims:

1-30. (Canceled)

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.

32. (New) The method of claim 31, wherein the second treatment regimen comprises mechanical ventilation.

33. (New) The method of claim 31, wherein the second treatment regimen does not comprise administration of inhaled nitric oxide.

34. (New) The method of claim 31, wherein the second treatment regimen comprises beginning administration of inhaled nitric oxide, but discontinuing the administration upon determining that inhaling nitric oxide has increased the second patient's pulmonary capillary wedge pressure (PCWP), the discontinuation being at a point before the second patient has received 14 days of inhaled nitric oxide administration and before the second patient's hypoxia has resolved.

35. (New) The method of claim 31, wherein the second treatment regimen comprises beginning administration of inhaled nitric oxide, but discontinuing the administration upon determining that inhaling nitric oxide has induced pulmonary edema in the second patient, the discontinuation being at a point before the second patient has received 14 days of inhaled nitric oxide administration and before the second patient's hypoxia has resolved.

36. (New) The method of claim 31, comprising performing a diagnostic process to identify the second patient as having hypoxic respiratory failure.

37. (New) The method of claim 36, wherein the diagnostic process comprises echocardiography.

38. (New) The method of claim 31, wherein the first and second patients are term or near-term neonates.

39. (New) The method of claim 31, wherein the selection of the second treatment regimen is based not only on a determination that the second patient is at particular risk of pulmonary edema, but also on a determination that the second patient is at particular risk of other serious adverse events, upon treatment with inhaled nitric oxide.

40. (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;

(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 administration of inhaled nitric oxide, and does comprise one or more other therapies selected from vasodilators, intravenous fluids, bicarbonate therapy and mechanical ventilation.

41. (New) The method of claim 40, wherein the second treatment regimen comprises mechanical ventilation.

42. (New) The method of claim 40, comprising performing a diagnostic process to identify the second patient as having hypoxic respiratory failure.

43. (New) The method of claim 42, wherein the diagnostic process comprises echocardiography.

44. (New) The method of claim 40, wherein the second patient is a term or near-term neonate.

45. (New) The method of claim 40, wherein the selection of the second treatment regimen is based not only on a determination that the second patient is at particular risk of

pulmonary edema, but also on a determination that the second patient is at particular risk of other serious adverse events, upon treatment with inhaled nitric oxide.

46. (New) A method of improving the safety of treating pulmonary hypertension in pediatric patients by reducing the risk of inducing pulmonary edema, the method comprising:

(a) identifying a pediatric patient having pulmonary hypertension and pre-existing left ventricular dysfunction;

(b) determining that, because the patient has pre-existing left ventricular dysfunction, the patient is at particular risk of increased PCWP leading to pulmonary edema, when treated with inhaled nitric oxide;

(c) treating the patient with 20 ppm inhaled nitric oxide;

(d) determining that the patient's PCWP increased during the treatment; and

(e) based on the determinations of (b) and (d), discontinuing the inhaled nitric oxide treatment.

47. (New) The method of claim 46, wherein the pulmonary hypertension is associated with hypoxia, and the discontinuation occurs at a point before the patient has received 14 days of inhaled nitric oxide administration and before the patient's hypoxia has resolved.

48. (New) The method of claim 46, wherein the discontinuation is based not only on a determination that the patient is at particular risk of increased PCWP leading to pulmonary edema, but also on a determination that the patient is at particular risk of other serious adverse events, upon treatment with inhaled nitric oxide.

49. (New) The method of claim 46, comprising performing a diagnostic process to identify the patient as having pulmonary hypertension.

50. (New) The method of claim 46, wherein the patient is a neonate.

51. (New) The method of claim 46, wherein the patient is a term or near-term neonate.

52. (New) The method of claim 46, wherein the patient's pulmonary hypertension is associated with hypoxic respiratory failure.

53. (New) The method of claim 52, wherein the patient is a neonate.

54. (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 neonatal patient as having hypoxic respiratory failure and pre-existing left ventricular dysfunction;

(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).

55. (New) The method of claim 54, wherein the discontinuation occurs at a point before the patient has received 14 days of inhaled nitric oxide administration and before the patient's hypoxia has resolved.

56. (New) The method of claim 54, comprising performing a diagnostic process to identify the patient as having hypoxic respiratory failure.

57. (New) The method of claim 56, wherein the diagnostic process comprises echocardiography.

58. (New) The method of claim 54, wherein the patient is a term or near-term neonate.

59. (New) The method of claim 55, wherein the patient is a term or near-term neonate.

60. (New) The method of claim 54, wherein the discontinuation is due not only to the determination that the patient is at particular risk of pulmonary edema, but also due to a determination that the patient is at particular risk of other serious adverse events, upon treatment with inhaled nitric oxide.

REMARKS

The above amendment cancels all of the original claims 1-30 and replaces them with new claims 31-60. Support for the new claims can be found throughout the original specification and claims (including the specification and claims of the original grandparent application (USSN 12/494,598) filed June 30, 2009)): for example, at paragraphs [0005], [0008], [0009], [0014], [0016], [0018], [0019], [0021] (which incorporates by reference the prescribing information for INOmax®), [0034], [0051], [0052], [0062] (including the table that is now numbered Table 7), and [0065], and in original claims 1, 4, 6, 8, 9, and 24. The amendment also amends the title and abstract. No new matter has been added by this amendment.

STATEMENT OF SUBSTITUTE SPECIFICATION UNDER 37 C.F.R. § 1.125

Pursuant to 37 C.F.R. § 1.125, Applicants submit a substitute specification encompassing changes being made to the specification filed on August 7, 2014. The specification is amended to revise the title, to add the priority information, to correct typographical errors, and to recite some of the text from the 2009 prescribing information for INOmax® nitric oxide for inhalation that had been incorporated by reference in the earliest priority application filed in 2009. This substitute specification introduces no new matter to the specification filed on August 7, 2014. Applicants request entry of the substitute specification.

Also attached is a marked-up version of the substitute specification, showing the changes that have been made.

Applicant asks that all claims be examined in view of the amendment to the claims.

The excess claims fee of $610 is being paid with this reply on the Electronic Filing System. Apply this and any other necessary charges or credits to Deposit Account 06-1050, referencing the above attorney docket number.

Respectfully submitted,

Date: August 13, 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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ABSTRACT

Disclosed are methods of reducing the risk that a medical treatment comprising inhalation of nitric oxide gas will induce an increase in pulmonary capillary wedge pressure in pediatric patients, leading to pulmonary edema. The methods include avoiding or discontinuing administration of inhaled nitric oxide to a pediatric patient determined to have pre-existing left ventricular dysfunction but who otherwise is a candidate for inhaled nitric oxide treatment (e.g., for pulmonary hypertension), and administering inhaled nitric oxide to pediatric patients who are candidates for such treatment and who are determined not to have pre-existing left ventricular dysfunction.

Electronic Patent Application Fee Transmittal

Application Number:	14454373
Filing Date:	
Title of Invention:	Methods of Treating Term and Near-Term Neonates Having Hypoxic Respiratory Failure Associated with Clinical or Echocardiographic Evidence of Pulmonary Hypertension
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:				
Claims in excess of 20	2202	10	40	400
Independent Claims in Excess of 3	2201	1	210	210
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Miscellaneous:				
		Total in USD ($)		**610**

Electronic Acknowledgement Receipt

EFS ID:	19860087
Application Number:	14454373
International Application Number:	
Confirmation Number:	3860
Title of Invention:	Methods of Treating Term and Near-Term Neonates Having Hypoxic Respiratory Failure Associated with Clinical or Echocardiographic Evidence of Pulmonary Hypertension
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:	13-AUG-2014
Filing Date:	
Time Stamp:	18:23:09
Application Type:	Utility under 35 USC 111(a)

Payment information:

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Payment Type	Deposit Account
Payment was successfully received in RAM	$610
RAM confirmation Number	4596
Deposit Account	061050
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Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)

1	Transmittal Letter	IDS.pdf	62556 2a2c3386abb4cdf58ebb0c58ac457fdec6ceda46	no	1
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2	Information Disclosure Statement (IDS) Form (SB08)	SB08.pdf	615615 8f7715b6ea606d512b1c5d7ac25a1a6903acc309	no	8
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Multipart Description/PDF files in .zip description

Document Description	Start	End
Preliminary Amendment	1	1
Specification	2	2
Abstract	3	3
Claims	4	9
Applicant Arguments/Remarks Made in an Amendment	10	11
Abstract	12	12

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6	Fee Worksheet (SB06)	fee-info.pdf	31653 e84e00ef96199aab887c06de543491176e552bc2	no	2
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New Applications Under 35 U.S.C. 111
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National Stage of an International Application under 35 U.S.C. 371
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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	Conf. No. :	3860
Serial No.	:	14/454,373		
Filed	:	August 7, 2014		
Title	:	METHODS FOR TREATING PATIENTS WHO ARE CANDIDATES FOR INHALED NITRIC OXIDE TREATMENT		

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

THIRD INFORMATION DISCLOSURE STATEMENT

Please consider the references listed on the enclosed PTO-SB-08 Form. Under 35 USC §120, this application relies on the earlier filing dates of application serial numbers 12/494,598, filed on June 30, 2009; 12/820,866, filed on June 22, 2010; 12/821,041, filed on June 22, 2010; 13/651,660, filed on October 15, 2012; 13/683,417, filed on November 21, 2012; 13/683,444, filed on November 21, 2012; and 14/451,057, filed on August 4, 2014. The cited references were submitted to and/or cited by the Office in one or more of the prior applications and therefore are not provided in this application.

This statement is being filed within three months of the filing date of the application. Apply any necessary charges or credits to Deposit Account 06-1050, referencing the above attorney docket number.

Respectfully submitted,

Date: August 13, 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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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	
	Examiner Name	
	Attorney Docket Number	26047-0003011

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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	
	Examiner Name	
	Attorney Docket Number	26047-0003011

	1	Konduri et al., "A Randomized Trial of Early Versus Standard Inhaled Nitric Oxide Therapy in Term and Near-Term Newborn Infants with Hypoxic Respiratory Failure," Pediatrics, Vol. 113 No. 3, pages 559-564 (2004)	☐
	2	Krasuski et al., "Inhaled Nitric Oxide Selectively Dilates Pulmonary Vasculature in Adult Patients With Pulmonary Hypertension, Irrespective of Etiology," Journal of the American College of Cardiology (JACC), Vol. 36, No. 7, pages 2204-2211 (2000)	☐
	3	Krohn, "Effect of inhaled nitric oxide on left ventricular and pulmonary vascular function," The Journal of Thoracic and Cardiovascular Surgery, Vol. 117(1), pages 195-196 (1999)	☐
	4	Kulik, "Inhaled nitric oxide in the management of congenital heart disease," Current Opinion in Cardiology, Vol. 11, pages 75-80 (1996)	☐
	5	Lavigne et al., "Cardiovascular Outcomes of Pediatric Seroreverters Perinatally Exposed to HAART," Cardiovascular Toxicology, Vol. 4, pages 187-197 (2004)	☐
	6	Letter of Acceptance for AU 2010202422, dated 10/7/2010	☐
	7	Letter of acceptance of AU application 2009202685, dated 08/10/2010, 3 pages	☐
	8	Lipschultz, "The effect of dexrazoxane on myocardial injury in doxorubicin-treated children with acute lymphoblastic leukemia," New England Journal of Medicine, Vol. 351, pages 145-153 (2004)	☐
	9	Lipschultz, "The incidence of pediatric cardiomyopathy in two regions of the United States," New England Journal of Medicine, April 24, 2003. <<http://www.nejm.org/doi/full/10.1056/NEJMoa021715>>"	☐
	10	Lipshultz, "Ventricular dysfunction clinical research in infants, children and adolescents," Progress in Pediatric Cardiology, Vol. 12, pages 1-28 (2000)	☐
	11	Lipshultz, "Chronic Progressive Cardiac Dysfunction Years After Doxorubicin Therapy for Childhood Acute Lymphoblastic Leukemia," Journal of Clinical Oncology, Vol. 23, No 12, 8 pages (2005)	☐

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	
	Examiner Name	
	Attorney Docket Number	26047-0003011

	12	Lipshultz, "Clinical research directions in pediatric cardiology," Current Opinion in Pediatrics, Vol. 21, pages 585-593 (2009)	☐
	13	Lipshultz, "Establishing norms for echocardiographic measurement of cardiovascular structures and function in children," J. Appl. Physiol., Vol. 99, pages 386-388 (2005)	☐
	14	Lipshultz et al., "Cardiovascular status of infants and children of women infected with HIV-1 (P2C2 HIV): a cohort study," The Lancet, Vol. 360, pages 368-373 (2002)	☐
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	Application Number	14454373
	Filing Date	2014-08-07
	First Named Inventor	Baldassarre
	Art Unit	
	Examiner Name	
	Attorney Docket Number	26047-0003011

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CERTIFICATION STATEMENT

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

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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.

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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		Date (YYYY-MM-DD)	2014-08-04
Name/Print	Janis K. Fraser	Registration Number	34819

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METHODS FOR IMPROVING THE SAFETY OF TREATING PEDIATRIC PATIENTS WHO ARE CANDIDATES FOR INHALED NITRIC OXIDE TREATMENT~~METHODS OF TREATING TERM AND NEAR-TERM NEONATES HAVING HYPOXIC RESPIRATORY FAILURE ASSOCIATED WITH CLINICAL OR ECHOCARDIOGRAPHIC EVIDENCE OF PULMONARY HYPERTENSION~~

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] ~~Not applicable.~~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.

BACKGROUND OF THE INVENTION

[0003] INOmax®, (nitric oxide) for inhalation is an approved drug product for the treatment of term and near-term (>34 weeks gestation) neonates having hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension.

[0004] The use of inhaled NO (iNO) has been studied and reported in the literature. (Kieler-Jensen M et al., 1994, Inhaled Nitric Oxide in the Evaluation of Heart Transplant Candidates with Elevated Pulmonary Vascular Resistance, *J Heart Lung Transplantation* 13:366-375; Pearl RG et al., 1983, Acute Hemodynamic Effects of Nitroglycerin in Pulmonary Hypertension, *American College of Physicians* 99:9-13; Ajami GH et al., 2007, Comparison of the Effectiveness of Oral Sildenafil Versus Oxygen Administration as a Test for Feasibility of Operation for Patients with Secondary Pulmonary Arterial Hypertension, *Pediatr Cardiol*; Schulze-Neick I et al., 2003, Intravenous Sildenafil Is a Potent Pulmonary Vasodilator in Children With Congenital Heart Disease, *Circulation* 108(Suppl II):II-167-II-173; Lepore JJ et al., 2002, Effect of Sildenafil on the Acute Pulmonary Vasodilator Response to Inhaled Nitric Oxide in Adults with Primary Pulmonary Hypertension, *The American Journal of Cardiology* 90:677-680; and Ziegler JW et al., 1998, Effects of Dipyridamole and Inhaled Nitric Oxide in Pediatric Patients with Pulmonary Hypertension, *American Journal of Respiratory and Critical Care Medicine* 158:1388-95).

SUMMARY OF THE INVENTION

[0005] One aspect of the invention relates to a pre-screening methodology or protocol having exclusionary criteria to be evaluated by a medical provider prior to treatment of a patient with iNO. One objective of the invention is to evaluate and possibly exclude from treatment patients eligible for treatment with iNO, who have pre-existing left ventricular dysfunction (LVD). Patients who have pre-existing LVD may experience, and are at risk of, an increased rate of adverse events or serious adverse events (e.g., pulmonary edema) when treated with iNO.

Such patients may be characterized as having a pulmonary capillary wedge pressure (PCWP) greater than 20 mm Hg, and should be evaluated on a case-by-case basis with respect to the benefit versus risk of using iNO as a treatment option.

[0006] Accordingly, one aspect of the invention includes a method of reducing the risk or preventing the occurrence, in a human patient, of an adverse event (AE) or a serious adverse event (SAE) associated with a medical treatment comprising inhalation of nitric oxide, said method comprising the steps or acts of (a) providing pharmaceutically acceptable nitric oxide gas to a medical provider; and[[,]] (b) informing the medical provider that excluding human patients who have pre-existing left ventricular dysfunction from said treatment reduces the risk or prevents the occurrence of the adverse event or the serious adverse event associated with said medical treatment.

[0007] Further provided herein is a method of reducing the risk or preventing the occurrence, in a human patient, of an adverse event or a serious adverse event associated with a medical treatment comprising inhalation of nitric oxide, said method comprising the steps or acts of (a[[.]]) providing pharmaceutically acceptable nitric oxide gas to a medical provider; and[[,]] (b[[.]]) informing the medical provider that human patients having pre-existing left ventricular dysfunction experience an increased risk of serious adverse events associated with said medical treatment.

[0008] Another aspect of the invention is a method of reducing one or more of an AE or a SAE in an intended patient population in need of being treated with iNO comprising the steps or acts of (a[[.]]) identifying a patient eligible for iNO treatment; (b) evaluating and screening the patient to identify if the patient has pre-existing LVD, and (c) excluding from iNO treatment a patient identified as having pre-existing LVD.

[0009] Another aspect of the invention is a method of reducing the risk or preventing the occurrence, in a patient, of one or more of an AE or a SAE associated with a medical treatment comprising iNO, the method comprising the steps or acts of (a[[.]]) identifying a patient in need of receiving iNO treatment; (b[[.]]) evaluating and screening the patient to identify if the patient has pre-existing LVD; and (c[[.]])_administering iNO if the patient does not have pre-existing LVD, thereby reducing the risk or preventing the occurrence of the AE or the SAE associated with the iNO treatment. Alternatively, step (c) may comprise further evaluating the risk versus

benefit of utilizing iNO in a patient where the patient[[s]] has clinically significant LVD before administering iNO to the patient.

[0010] In an exemplary embodiment of the method, the method further comprises informing the medical provider that there is a risk associated with using inhaled nitric ~~oxides~~ oxide in human patients who have preexisting or clinically significant left ventricular dysfunction and that such risk should be evaluated on a case by case basis.

[0011] In another exemplary embodiment of the method, the method further comprises informing the medical provider that there is a risk associated with using inhaled nitric oxide in human patients who have left ventricular dysfunction.

[0012] In an exemplary embodiment of the methods described herein, a patient having pre-existing LVD is characterized as having PCWP greater than 20 mm Hg.

[0013] In an exemplary embodiment of the method, the patients having pre-existing LVD demonstrate [[ ]]a PCWP $\geq$ 20 mm Hg.

[0014] In another exemplary embodiment of the method, the iNO treatment further comprises inhalation of oxygen (O_2) or concurrent ventilation.

[0015] In another exemplary embodiment of the method, the patients having pre-existing LVD have one or more of diastolic dysfunction, hypertensive cardiomyopathy, systolic dysfunction, ischemic cardiomyopathy, viral cardiomyopathy, idiopathic cardiomyopathy, autoimmune disease related cardiomyopathy, drug-related cardiomyopathy, toxin-related cardiomyopathy, structural heart disease, valvular heart disease, congenital heart disease, or[[,]] associations thereof.

[0016] In another exemplary embodiment of the method, the patient population comprises children.

[0017] In another exemplary embodiment of the method, the patient population comprises adults.

[0018] In another exemplary embodiment of the method, the patients who have pre-existing LVD are at risk of experiencing ~~and~~ an increased rate of one or more AEs or SAEs selected from pulmonary edema, hypotension, cardiac arrest, electrocardiogram changes, hypoxemia, hypoxia, bradycardia or associations thereof.

[0019] In another exemplary embodiment of the method, the intended patient population in need of being treated with inhalation of nitric oxide has one or more of idiopathic pulmonary

arterial hypertension characterized by a mean pulmonary artery pressure (PAPm) > 25 mm Hg at rest, PCWP ≤ 15 mm Hg, and[[,]] a pulmonary vascular resistance index (PVRI) > 3 u·m^2; congenital heart disease with pulmonary hypertension repaired and unrepaired characterized by PAPm > 25 mm Hg at rest and PVRI > 3 u·m^2; cardiomyopathy characterized by PAPm > 25 mm Hg at rest and PVRI > 3 u·m^2; or[[,]] the patient is scheduled to undergo right heart catheterization to assess pulmonary vasoreactivity by acute pulmonary vasodilatation testing.

[0020] In another exemplary embodiment of any of the above methods, the method further comprises reducing left ventricular afterload to minimize or reduce the risk of the occurrence of an adverse event or serious adverse event being pulmonary edema in the patient. The left ventricular afterload may be minimized or reduced by administering a pharmaceutical dosage form comprising nitroglycerin or calcium channel blocker to the patient. The left ventricular afterload may also be minimized or reduced using an intra-aortic balloon pump.

DETAILED DESCRIPTION OF THE EXEMPLARY EMBODIMENTS

[0021] INOmax® (nitric oxide) for inhalation was approved for sale in the United States by the U.S. Food and Drug Administration ("FDA") in 1999. Nitric oxide, the active substance in INOmax®, is a selective pulmonary vasodilator that increases the partial pressure of arterial oxygen (PaO_2) by dilating pulmonary vessels in better ventilated areas of the lung, redistributing pulmonary blood flow away from the lung regions with low ventilation/perfusion (V/Q) ratios toward regions with normal ratios. INOmax® significantly improves oxygenation, reduces the need for extracorporeal oxygenation and is indicated to be used in conjunction with ventilatory support and other appropriate agents. The ~~current~~ FDA-approved prescribing information for INOmax® in effect in 2009 is incorporated herein by reference in its entirety. The DOSAGE section of the prescribing information for INOmax® states that the recommended dose of INOmax® is 20 ppm, and that treatment should be maintained up to 14 days or until the underlying oxygen desaturation has resolved and the neonate is ready to be weaned from INOmax® therapy. The ADMINISTRATION section of the prescribing information says that the safety and effectiveness of inhaled nitric oxide have been established in a population receiving other therapies for hypoxic respiratory failure, including vasodilators, intravenous fluids, bicarbonate therapy, and mechanical ventilation. The CONTRAINDICATIONS section

of the prescribing information states that INOmax® should not be used in the treatment of neonates known to be dependent on right-to-left shunting of blood.

[0022] INOmax® is a gaseous blend of NO and nitrogen (0.08% and 99.92% respectively for 800 ppm; and 0.01% and 99.99% respectively for 100 ppm) and is supplied in aluminium cylinders as a compressed gas under high pressure. In general, INOmax® is administered to a patient in conjunction with ventilatory support and O_2. Delivery devices suitable for the safe and effective delivery of gaseous NO for inhalation include the INOvent®, INOmax DS®, INOpulse®, INOblender®, or other suitable drug delivery and regulation devices or components incorporated therein, or other related processes, which are described in various patent documents including USPNs 5,558,083; 5,732,693; 5,752,504; 5,732,694; 6,089,229; 6,109,260; 6,125,846; 6,164,276; 6,581,592; 5,918,596; 5,839,433; 7,114,510; 5,417;950; 5,670,125; 5,670,127; 5,692,495; 5,514,204; 7,523,752; 5,699,790; 5,885,621; US Patent Application Serial Nos. 11/355,670 (US 2007/0190184); 10/520,270 (US 2006/0093681); 11/401,722 (US 2007/0202083); 10/053,535 (US 2002/0155166); 10/367,277 (US 2003/0219496); 10/439,632 (US 2004/0052866); 10/371,666 (US 2003/0219497); 10/413,817 (US 2004/0005367); 12/050,826 (US 2008/0167609); and PCT/US2009/045266, all of which are incorporated herein by reference in their entirety.

[0023] Such devices deliver INOmax® into the inspiratory limb of the patient breathing circuit in a way that provides a constant concentration of NO to the patient throughout the inspired breath. Importantly, suitable delivery devices provide continuous integrated monitoring of inspired O[[2]]$_2$, NO_2 and NO, a comprehensive alarm system, a suitable power source for uninterrupted NO delivery, and a backup NO delivery capability.

[0024] As used herein, the term "children" (and variations thereof) includes those being around 4 weeks to 18 years of age.

[0025] As used herein, the term "adult" (and variations thereof) includes those being over 18 years of age.

[0026] As used herein, the terms "adverse event" [[or]]and "AE" (and variations thereof) mean any untoward occurrence in a subject[[,]] or clinical investigation subject administered a pharmaceutical product (such as nitric oxide) and which does not necessarily have a causal relationship with such treatment. An adverse event can therefore be any unfavorable and

unintended sign (including an abnormal laboratory finding), symptom, or disease temporarily associated with the use of a medicinal/investigational product, whether or not related to the investigational product. A relationship to the investigational product is not necessarily proven or implied. However, abnormal values are not reported as adverse events unless considered clinically significant by the investigator.

[0027] As used herein, the terms "adverse drug reaction" [[or]]and "ADR" (and variations thereof) mean any noxious and unintended response to a medicinal product related to any dose.

[0028] As used herein, the terms "serious adverse event" [[or]]and "SAE" (or "serious adverse drug reaction" [[or]]and "serious ADR") (and variations thereof) mean a significant hazard or side effect, regardless of the investigator's opinion on the relationship to the investigational product. A serious adverse event or reaction is any untoward medical occurrence that at any dose: results in death; is life-threatening (which refers to an event/reaction where the patient was at risk of death at the time of the event/reaction, however this does not refer to an event/reaction that hypothetically may have caused death if it were more severe); requires inpatient hospitalization or results in prolongation of existing hospitalization; results in persistent or significant disability/incapacity; is a congenital anomaly/birth defect; or[[,]] is a medically important event or reaction. Medical and scientific judgment is exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed above--these are also considered serious. Examples of such medical events include cancer, allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in hospitalizations, or the development of drug dependency or drug abuse. Serious clinical laboratory abnormalities directly associated with relevant clinical signs or symptoms are also reported.

[0029] Left Ventricular Dysfunction. Patients having pre-existing LVD may be described in general as those with elevated pulmonary capillary wedge pressure, including those with diastolic dysfunction (including hypertensive cardiomyopathy), those with systolic

dysfunction, including those with cardiomyopathies (including ischemic or viral cardiomyopathy, or idiopathic cardiomyopathy, or autoimmune disease related cardiomyopathy, and side effects due to drug related or toxic-related cardiomyopathy), or structural heart disease, valvular heart disease, congenital heart disease, idiopathic pulmonary arterial hypertension, pulmonary hypertension and cardiomyopathy, or associations thereof. Identifying patients with pre-existing LVD is known to those skilled in the medicinal arts, and such techniques for example may include assessment of clinical signs and symptoms of heart failure, or echocardiography diagnostic screening.

[0030] Pulmonary Capillary Wedge Pressure. Pulmonary capillary wedge pressure, or "PCWP", provides an estimate of left atrial pressure. Identifying patients with pre-existing PCWP is known to those skilled in the medicinal arts, and such techniques for example may include ~~measure~~ measuring by inserting balloon-tipped, multi-lumen catheter (also known as a Swan-Ganz catheter). ~~Measure~~ Measurement of PCWP may be used as a means to diagnose the severity of LVD (sometimes also referred to as left ventricular failure). PCWP is also a desired measure when evaluating pulmonary hypertension. Pulmonary hypertension is often caused by an increase in pulmonary vascular resistance (PVR), but may also arise from increases in pulmonary venous pressure and pulmonary blood volume secondary to left ventricular failure or mitral or aortic valve disease.

[0031] In cardiac physiology, the term "afterload" is used to mean the tension produced by a chamber of the heart in order to contract. If the chamber is not mentioned, it is usually assumed to be the left ventricle. However, the strict definition of the term relates to the properties of a single cardiac myocyte. It is therefore ~~only~~ of direct relevance only in the laboratory; in the clinic, the term end-systolic pressure is usually more appropriate, although not equivalent.

[0032] The ~~terms~~ term "left ventricular afterload" (and variations thereof) ~~refer~~ refers to the pressure that the chamber of the heart has to generate in order to eject blood out of the chamber. Thus, it is a consequence of the aortic pressure, since the pressure in the ventricle must be greater than the systemic pressure in order to open the aortic valve. Everything else held equal, as afterload increases, cardiac output decreases. Disease processes that increase the left ventricular afterload include increased blood pressure and aortic valve disease.

Hypertension (i~~I~~ncreased blood pressure) increases the left ventricular afterload because the left ventricle has to work harder to eject blood into the aorta. This is because the aortic valve won't open until the pressure generated in the left ventricle is higher than the elevated blood pressure. Aortic stenosis increases the afterload because the left ventricle has to overcome the pressure gradient caused by the stenotic aortic valve in addition to the blood pressure in order to eject blood into the aorta. For instance, if the blood pressure is 120/80, and the aortic valve stenosis creates a trans-valvular gradient of 30 mmHg, the left ventricle has to generate a pressure of 110 mmHg in order to open the aortic valve and eject blood into the aorta. Aortic insufficiency increases afterload because a percentage of the blood that is ejected forward regurgitates back through the diseased aortic valve. This leads to elevated systolic blood pressure. The diastolic blood pressure would fall, due to regurgitation. This would result in an ~~increase~~ increased pulse pressure. Mitral regurgitation decreases the afterload. During ventricular systole, the blood can regurgitate through the diseased mitral valve as well as be ejected through the aortic valve. This means that the left ventricle has to work less to eject blood, causing a decreased afterload. Afterload is largely dependent upon aortic pressure.

[0033] An intra-aortic balloon pump (IABP) is a mechanical device that is used to decrease myocardial oxygen demand while at the same time increasing cardiac output. By increasing cardiac output it also increases coronary blood flow and therefore myocardial oxygen delivery. It consists of a cylindrical balloon that sits in the aorta and counterpulsates. That is, it actively deflates in systole, increasing forward blood flow by reducing afterload ~~thus~~, and actively inflates in diastole, increasing blood flow to the coronary arteries. These actions have the combined result of decreasing myocardial oxygen demand and increasing myocardial oxygen supply. The balloon is inflated during diastole by a computer controlled mechanism, usually linked to either an ECG or a pressure transducer at the distal tip of the catheter; some IABPs, such as the Datascope System 98XT, allow for asynchronous counterpulsation at a set rate, though this setting is rarely used. The computer controls the flow of helium from a cylinder into and out of the balloon. Helium is used because its low viscosity allows it to travel quickly through the long connecting tubes, and it has a lower risk of causing a harmful embolism should the balloon rupture while in use. Intraaortic balloon counterpulsation is used in situations when the heart's own cardiac output is insufficient to meet the oxygenation demands of the body.

These situations could include cardiogenic shock, severe septic shock, post cardiac surgery and numerous other situations.

[0034] Patients eligible for treatment with iNO. In general, patients approved for treatment of iNO are term and near-term (>34 weeks gestation) neonates having hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension, a condition also known as persistent pulmonary hypertension in the newborn (PPHN). Due to the selective, non-systemic nature of iNO to reduce pulmonary hypertension, physicians skilled in the art further employ INOmax® to treat or prevent pulmonary hypertension and improve blood O_2 levels in a variety of other clinical settings, including in both pediatric and adult patients suffering from acute respiratory distress syndrome (ARDS), pediatric and adult patients undergoing cardiac or transplant surgeries, pediatric and adult patients for testing to diagnose reversible pulmonary hypertension, and in pediatric patients with congenital diaphragmatic hernia. In most, if not all, of these applications, INOmax® acts by preventing or treating reversible pulmonary vasoconstriction, reducing pulmonary arterial pressure and improving pulmonary gas exchange.

[0035] A small proportion of INOmax® sales stem from its use by clinicians in a premature infant population. In these patients, INOmax® is generally utilized by physicians as a rescue therapy primarily to vasodilate the lungs and improve pulmonary gas exchange. Some physicians speculate that INOmax® therapy may promote lung development and/or reduce or prevent the future development of lung disease in a subset of these patients. Although the precise mechanism(s) responsible for the benefits of INOmax® therapy in these patients is not completely understood, it appears that the benefits achieved in at least a majority of these patients are due to the ability of INOmax® to treat or prevent reversible pulmonary vasoconstriction.

[0036] In clinical practice, the use of INOmax® has reduced or eliminated the use of high risk systemic vasodilators for the treatment of PPHN. INOmax®, in contrast to systemic vasodilators, specifically dilates the pulmonary vasculature without dilating systemic blood vessels. Further, iNO preferentially vasodilates vessels of aveoli that are aerated, thus improving V/Q matching. In contrast, systemic vasodilators may increase blood flow to atelectatic (deflated or collapsed) alveoli, thereby increasing V/Q mismatch and worsening

arterial oxygenation. (*See* Rubin LJ, Kerr KM, Pulmonary Hypertension, in *Critical Care Medicine: Principles of Diagnosis and Management in the Adult, 2d Ed.*, Parillo JE, Dellinger RP (eds.), Mosby, Inc. 2001, pp. 900-09 at 906; Kinsella JP, Abman SH, The Role of Inhaled Nitric Oxide in Persistent Pulmonary Hypertension of the Newborn, in *Acute Respiratory Care of the Neonate: A Self-Study Course, 2d Ed.*, Askin DF (ed.), NICU Ink Book Publishers, 1997, pp. 369-378 at 372-73).

[0037] INOmax® also possesses highly desirable pharmacokinetic properties as a lung-specific vasodilator when compared to other ostensibly "pulmonary-specific vasodilators." For example, the short half-life of INOmax® allows INOmax® to exhibit rapid "on" and "off" responses relative to INOmax® dosing, in contrast to non-gaseous alternatives. In this way, INOmax® can provide physicians with a useful therapeutic tool to easily control the magnitude and duration of the pulmonary vasodilatation desired. Also, the nearly instantaneous inactivation of INOmax® in the blood significantly reduces or prevents vasodilatation of non-pulmonary vessels.

[0038] The pivotal trials leading to the approval of INOmax® were the CINRGI and NINOS study.

[0039] CINRGI study. (See Davidson et al., March 1998, 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, No. 3, p. 325).

[0040] This study was a double-blind, randomized, placebo-controlled, multicenter trial of 186 term and near-term neonates with pulmonary hypertension and hypoxic respiratory failure. The primary objective of the study was to determine whether INOmax® would reduce the receipt of extracorporeal membrane oxygenation (ECMO) in these patients. Hypoxic respiratory failure was caused by meconium aspiration syndrome (MAS) (35%), idiopathic persistent pulmonary hypertension of the newborn (PPHN) (30%), pneumonia/sepsis (24%), or respiratory distress syndrome (RDS) (8%). Patients with a mean PaO_2 of 54 mm Hg and a mean oxygenation index (OI) of 44 cm H_2O/mm Hg were randomly assigned to receive either 20 ppm INOmax® (n=97) or nitrogen gas (placebo; n=89) in addition to their ventilatory support. Patients that exhibited a $PaO_2 > 60$ mm Hg and a pH < 7.55 were weaned to 5 ppm

INOmax® or placebo. The primary results from the CINRGI study are presented in Table [[4]]1. ECMO was the primary endpoint of the study.

Table 1: Summary of Clinical Results from CINRGI Study

	Placebo	INOmax®	P value
Death or ECMO	51/89 (57%)	30/97 (31%)	<0.001
Death	5/89 (6%)	3/97 (3%)	0.48

[0041] Significantly fewer neonates in the ECMO group required ECMO, and INOmax® significantly improved oxygenation, as measured by PaO_2, OI, and alveolar-arterial gradient.

[0042] NINOS study. (See Inhaled Nitric Oxide in Full-Term and Nearly Full-Term Infants with Hypoxic Respiratory Failure; NEJM, Vol. 336, No. 9, 597).

[0043] The Neonatal Inhaled Nitric Oxide Study (NINOS) group conducted a double-blind, randomized, placebo-controlled, multicenter trial in 235 neonates with hypoxic respiratory failure. The objective of the study was to determine whether iNO would reduce the occurrence of death and/or initiation of ECMO in a prospectively defined cohort of term or near-term neonates with hypoxic respiratory failure unresponsive to conventional therapy. Hypoxic respiratory failure was caused by meconium aspiration syndrome (MAS; 49%), pneumonia/sepsis (21%), idiopathic primary pulmonary hypertension of the newborn (PPHN; 17%), or respiratory distress syndrome (RDS; 11%). Infants ≤ 14 days of age (mean, 1.7 days) with a mean PaO_2 of 46 mm Hg and a mean oxygenation index (OI) of 43 cm H_2O/mmHg were

initially randomized to receive 100% O_2 with (n=114) or without (n=121) 20 ppm NO for up to 14 days. Response to study drug was defined as a change from baseline in PaO_2 30 minutes after starting treatment (full response = > 20 mmHg, partial = 10–20 mm Hg, no response = < 10 mm Hg). Neonates with a less than full response were evaluated for a response to 80 ppm NO or control gas. The primary results from the NINOS study are presented in Table 2.

Table 2: Summary of Clinical Results from NINOS Study

	Control (n=121)	NO (n=114)	P value
Death or ECMO*, †	77 (64%)	52 (46%)	0.006
Death	20 (17%)	16 (14%)	0.60
ECMO	66 (55%)	44 (39%)	0.014

* Extracorporeal membrane oxygenation
† Death or need for ECMO was the study's primary end point

[0044] Adverse Events from CINRGI & NINOS. Controlled studies have included 325 patients on INOmax® doses of 5 to 80 ppm and 251 patients on placebo. Total mortality in the pooled trials was 11% on placebo and 9% on INOmax®, a result adequate to exclude INOmax® mortality being more than 40% worse than placebo.

[0045] In both the NINOS and CINRGI studies, the duration of hospitalization was similar in INOmax® and placebo-treated groups.

[0046] From all controlled studies, at least 6 months of follow-up is available for 278 patients who received INOmax® and 212 patients who received placebo. Among these patients, there was no evidence of an AE of treatment on the need for re-hospitalization, special medical services, pulmonary disease, or neurological ~~squeal~~sequelae.

[0047] In the NINOS study, treatment groups were similar with respect to the incidence and severity of intracranial hemorrhage, Grade IV hemorrhage, per ventricular leukomalacia, cerebral infarction, seizures requiring anticonvulsant therapy, pulmonary hemorrhage, or gastrointestinal hemorrhage.

[0048] The table below shows adverse reactions that occurred in at least 5% of patients receiving INOmax® in the CINRGI study. None of the differences in these adverse reactions were statistically significant when iNO patients were compared to patients receiving placebo.

Table 3: ADVERSE REACTIONS ON THE CINRGI TRIAL

Adverse Reaction	Placebo (n=89)	Inhaled NO (n=97)
Atelectasis	5 (4.8%)	7 (6.5%)
Bilirubinemia	6 (5.8%)	7 (6.5%)
Hypokalemia	5 (4.8%)	9 (8.3%)
Hypotension	3 (2.9%)	6 (5.6%)
Thrombocytopenia	20 (19.2%)	16 (14.8%)

[0049] Post-Marketing Experience. The following AEs have been reported as part of the post-marketing surveillance. These events have not been reported above. Given the nature of spontaneously reported post-marketing surveillance data, it is impossible to determine the actual incidence of the events or definitively establish their causal relationship to the drug. The listing is alphabetical: dose errors associated with the delivery system; headaches associated with environmental exposure of INOmax® in hospital staff; hypotension associated with acute withdrawal of the drug; hypoxemia associated with acute withdrawal of the drug; pulmonary edema in patients with CREST syndrome.

[0050] An analysis of AEs and SAEs from both the CINRGI and NINOS studies, in addition to post-marketing surveillance, did not suggest that patients who have pre-existing LVD could experience an increased risk of AEs or SAEs. Nor was it predictable to physicians skilled in the art that patients having pre-existing LVD (possibly identified as those patients having a PCWP greater than 20 mmHg) should be evaluated in view of the benefit versus risk of using iNO in patients with clinically significant LVD, and that these patients should be evaluated on a case by case basis.

EXAMPLE 1: INOT22 STUDY

[0051] The INOT22 study, 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 vasodilatory testing" was conducted both to ~~access~~ assess the safety and

effectiveness of INOmax® as a diagnostic agent in patients undergoing assessment of pulmonary hypertension (primary endpoint), and to confirm the hypothesis that iNO is selective for the pulmonary vasculature (secondary endpoint).

[0052] During, and upon final analysis of the INOT22 study results, applicants discovered that rapidly decreasing the pulmonary vascular resistance, via the administration of iNO to a patient in need of such treatment, may be detrimental to patients with concomitant, pre-existing LVD. Therefore, a precaution for patients with LVD was proposed to be included in amended prescribing information for INOmax®. Physicians were further informed to consider reducing left ventricular afterload to minimize the occurrence of pulmonary edema in patients with pre-existing LVD.

[0053] In particular, the INOT22 protocol studied consecutive children undergoing cardiac catheterization that were prospectively enrolled at 16 centers in the US and Europe. Inclusion criteria: 4 weeks to 18 years of age, pulmonary hypertension diagnosis, i.e. either idiopathic pulmonary hypertension (IPAH) or related to congenital heart disease (CHD) (repaired or unrepaired) or cardiomyopathy, with pulmonary vascular resistance index (PVRI) > 3 u-m^2. Later amendments, as discussed herein, added an additional inclusionary ~~criteria~~ criterion of a PCWP less than 20 [[gmm]]mm Hg. Patients were studied under general anaesthesia, or with conscious sedation, according to the practice of the investigator. Exclusion criteria: focal infiltrates on chest X-ray, history of intrinsic lung disease, and/or currently taking PDE-5 inhibitors, prostacyclin analogues or sodium nitroprusside. The study involved supplemental O_2 and NO for inhalation plus O_2 in the evaluation of the reactivity of the pulmonary vasculature during acute pulmonary vasodilator testing. Consecutive children undergoing cardiac catheterization were prospectively enrolled at 16 centers in the US and Europe. As hypotension is expected in these neonatal populations, the comparison between iNO and placebo groups is difficult to assess. A specific secondary endpoint was evaluated in study INOT22 to provide a more definitive evaluation.

[0054] The primary objective was to compare the response frequency with iNO and O_2 vs. O_2 alone; in addition, all subjects were studied with iNO alone. Patients were studied during five periods: Baseline 1, Treatment Period 1, Treatment Period 2, Baseline 2 and Treatment Period 3. All patients received all three treatments; treatment sequence was randomized by

center in blocks of 4; in Period 1, patients received either NO alone or O_2 alone, and the alternate treatment in Period 3. All patients received the iNO and O_2 combination treatment in Period 2. Once the sequence was assigned, treatment was unblinded. Each treatment was given for 10 minutes prior to obtaining hemodynamic measurements, and the Baseline Period 2 was at least 10 minutes.

[0055] Results for the intent-to-treat (ITT) population, defined as all patients who were randomized to receive drug, indicated that treatment with NO plus O_2 and O_2 alone significantly increased systemic vascular resistance index (SVRI) (Table 4). The change from baseline for NO plus O_2 was 1.4 Woods Units per meter^2 (WU·m^2) ($p = 0.007$) and that for O_2 was 1.3 WU·m^2 ($p = 0.004$). While the change from baseline in SVRI with NO alone was -0.2 WU·m^2 ($p = 0.899$) which demonstrates a lack of systemic effect.

Table 4: SVRI Change From Baseline by Treatment (Intent-to-Treat)

	Treatment		
SVRI ($WU \cdot m^2$)	**NO Plus O_2 (n=109)**	**O_2 (n=106)**	**NO (n=106)**
Baseline (room air)			
Mean	17.2	17.6	18.0
Standard Deviation (SD)	8.86	9.22	8.44
Median	15.9	16.1	16.2
Minimum, maximum	-7.6, 55.6	-7.6, 55.6	1.9, 44.8
Post-treatment			
Mean	18.7	18.9	17.8
SD	9.04	8.78	9.40
Median	17.1	17.1	15.4
Minimum, maximum	3.0, 47.4	3.9, 43.6	3.3, 50.7
Change From Baseline			
Mean	1.4	1.3	-0.2
SD	5.94	5.16	4.65
Median	1.2	1.0	0.2
Minimum, maximum	-20.5, 19.1	-18.1, 17.7	-12.5, 12.7
p-value[a]	0.007	0.004	0.899
Pairwise comparisons NO plus O_2 versus O_2, p=0.952 NO plus O_2 versus NO, p=0.014 O_2 versus NO, p=0.017			

[a] p-value from a Wilcoxon Signed Rank Test. Only patients with data to determine response at both treatments are included in this analysis.
Source: INOT22 CSR Table 6.4.1 and Appendix 16.2.6 (ATTACHMENT 1)

[0056] The ideal pulmonary vasodilator should reduce PVRI and/or PAPm while having no appreciable effect on systemic blood pressure or SVRI. In this case, the ratio of PVRI to SVRI would decrease, given some measure of the selectivity of the agent for the pulmonary vascular bed. The change in the ratio of PVRI to SVRI by treatment is shown in Table 5.

Table 5: Change in Ratio of PVRI to SVRI by Treatment (Intent-to-Treat)

	Treatment		
Ratio PVRI/SVRI	**NO Plus O_2 (n=108)**	**O_2 (n=105)**	**NO (n=106)**
Baseline			
Mean	0.6	0.5	0.6
SD	0.60	0.45	0.56
Median	0.5	0.5	0.4
Minimum, Maximum	-1.6, 4.7	-1.6, 1.8	0.0, 4.7
Post Treatment			
Mean	0.4	0.4	0.5
SD	0.31	0.31	0.46
Median	0.3	0.4	0.3
Minimum, Maximum	0.0, 1.3	0.0, 1.4	-1.2, 2.2
Change from Baseline			
Mean	-0.2	-0.1	-0.1
SD	0.52	0.31	0.54
Median	-0.1	-0.1	0.0
Minimum, Maximum	-4.4, 2.0	-1.6, 2.0	-4.4, 1.6
P Value[1]	< 0.001	< 0.001	0.002

[1] Wilcoxon Signed Rank Test
Source: INOT22 CSR Table 6.5.1 (ATTACHMENT 2)

[0057] All three treatments have a preferential effect on the pulmonary vascular bed, suggesting that all three are selective pulmonary vasodilators. The greatest reduction in the ratio was during treatment with NO plus O_2, possibly due to the decrease in SVRI effects seen with O_2 and NO plus O_2. These results are displayed as percent change in the ratio (See Table 6).

Table 6: Percent Change in Ratio of PVRI to SVRI by Treatment (Intent-to-Treat)

	Treatment		
Ratio PVRI/SVRI	**NO Plus O_2 (n=108)**	**O_2 (n=105)**	**NO (n=106)**
Baseline			
Mean	0.6	0.5	0.6
SD	0.60	0.45	0.56
Median	0.5	0.5	0.4
Minimum, Maximum	-1.6, 4.7	-1.6, 1.8	0.0, 4.7
Post Treatment			
Mean	0.4	0.4	0.5
SD	0.31	0.31	0.46
Median	0.3	0.4	0.3
Minimum, Maximum	0.0, 1.3	0.0, 1.4	-1.2, 2.2
Percent Change from Baseline			
Mean	-33.5	-19.3	-6.2
SD	36.11	34.59	64.04
Median	-34.0	-21.3	-13.8
Minimum, Maximum	-122.2, 140.1	-122.7, 93.3	-256.1, 294.1
P Value[1]	< 0.001	< 0.001	0.006

[1] Wilcoxon Signed Rank Test
Source: INOT22 CSR Table 6.5.2 (ATTACHMENT 3)

[0058] NO plus O_2 appeared to provide the greatest reduction in the ratio, suggesting that NO plus O_2 was more selective for the pulmonary vasculature than either agent alone.

[0059] Overview of Cardiovascular Safety. In the INOT22 diagnostic study, all treatments (NO plus O_2, O_2, and NO) were well-tolerated. Seven patients of 134 treated experienced an AE during the study. These included cardiac arrest, bradycardia, low cardiac output (CO) syndrome, elevated ST segment (the portion of an electrocardiogram between the end of the QRS complex and the beginning of the T wave) on the electrocardiography (ECG)

decreased O_2 saturation, hypotension, mouth hemorrhage and pulmonary hypertension (PH). The numbers of patients and events were too small to determine whether risk for AEs differed by treatment, diagnosis, age, gender or race. Eight patients are shown in Table 5 due to the time period in which events are reported. AEs were reported for 12 hours or until hospital discharge (which limits the period in which such events can be reported). There is technically no time limit in which SAEs are to be reported. So, there were 7 AEs during the study and at least one SAE after the study.

[0060] A total of 4 patients had AEs assessed as being related to study drug. These events included bradycardia, low CO syndrome, ST segment elevation on the ECG, low O_2 saturation, PH and hypotension. All but 2 AEs were mild or moderate in intensity and were resolved. Study treatments had slight and non-clinically significant effects on vital signs including heart rate, systolic arterial pressure and diastolic arterial pressure. When an investigator records an AE, they are required to say if (in their opinion) the event is related to the treatment or not. In this case, 4 of 7 were considered by the investigator to be related to treatment.

[0061] The upper limit of normal PCWP in children is 10-12 mm Hg and 15 mm Hg in adults. In INOT22, a baseline PCWP value was not included as exclusion criteria. However, after the surprising and unexpected identification of SAEs in the early tested patients, it was determined that patients with pre-existing LVD had an increased risk of experiencing an AE or SAE upon administration (e.g., worsening of left ventricular function due to the increased flow of blood through the lungs). Accordingly, the protocol for INOT22 was [[ ]]thereafter amended to exclude patients with a baseline PCWP greater than 20 mm Hg after one patient experienced acute circulatory collapse and died during the study. The value "20 mm Hg" was selected to avoid enrollment of a pediatric population with LVD such that they [[ ]]would be most likely at-risk for these SAEs.

[0062] SAEs were collected from the start of study treatment until hospital discharge or 12 hours, whichever occurred sooner. Three SAEs were reported during the study period, and a total of 7 SAEs were reported. Three of these were fatal SAEs and 4 were nonfatal (one of which led to study discontinuation). In addition, one non-serious AE also ~~lead~~ led to

discontinuation. A list of subjects who died, discontinued or experienced an SAE is provided in Table [[5]]7 below.

Table [[5]]7: Subjects that died, discontinued or experienced SAEs

Patient number	AE	Serious?	Fatal?	Discontinued treatment?
01020	Desaturation (hypoxia)	No	No	Yes
02002	Pulmonary edema	Yes	No	No
04001	Hypotension and cardiac arrest	Yes	Yes	No
04003	Hypotension and ECG changes	Yes	No	Yes
04008	Hypotension and hypoxemia	Yes	Yes	No
05002	Hypoxia and bradycardia (also pulmonary edema)	Yes	Yes	No
07003	Cardiac arrest	Yes	No	No
17001	Hypoxia	Yes	No	No

[0063] Two of the 3 fatal SAEs were deemed related to therapy. All 4 non-fatal SAEs were also considered related to therapy. The numbers of patients and events were too small to determine whether risk for SAEs differed by treatment, diagnosis, age, gender or race. At least two patients developed signs of pulmonary edema (subjects 05002 and 02002). This is of interest because pulmonary edema has previously been reported with the use of iNO in patients with LVD, and may be related to decreasing PVRI and overfilling of the left atrium. (Hayward CS et al., 1996, Inhaled Nitric Oxide in Cardiac Failure: Vascular Versus Ventricular Effects, *J Cardiovascular Pharmacology* 27:80-85; Bocchi EA et al., 1994, Inhaled Nitric Oxide Leading to Pulmonary Edema in Stable Severe Heart Failure, *Am J Cardiology* 74:70-72; and, Semigran MJ et al., 1994, Hemodynamic Effects of Inhaled Nitric Oxide in Heart Failure, *J Am Coll Cardiology* 24:982-988).

[0064] Although the SAE rate is within range for this population, it appears that patients with the most elevated PCWP at baseline had a disproportionately high number of these events. (Bocchi EA et al., 1994; Semigran MJ et al., 1994).

[0065] In the INOT22 study, 10 of the total 134 patients had a baseline PCWP $\geq$ 18 mm Hg (7.5%), of which[[,]] 3 subjects (04001, 02002 and 04003) had a SAE or were prematurely discontinued from the study (30%), compared to 6.5% for the entire cohort.

[0066] Although there were very few significant AEs in the INOT22 study, these events are consistent with the expected physiologic changes in patients with severe LVD. The events also corroborate prior observations that iNO is rapidly acting, selective for the pulmonary vasculature, and well-tolerated in most patients. The actual incidence of acute LVD during acute ventricular failure (AVT) is unknown. However, it is reasonable to expect that a significant number of patients are at-risk for an increased incidence of SAEs upon iNO treatment based upon the nature of the underlying nature of the illness, i.e., pulmonary hypertension and cardiovascular disease more generally. Thus, it would be advantageous to have physicians identify these patients prior to beginning iNO treatment, so that the physicians are alerted to this possible outcome.

[0067] Benefits and Risks Conclusions. The INOT22 study was designed to demonstrate the physiologic effects of iNO in a well defined cohort of children (i.e., intended patient population) with pulmonary hypertension using a high concentration, 80 ppm, of iNO, i.e., one that would be expected to have the maximal pharmacodynamic effect. INOT22 was the largest and most rigorous pharmacodynamic study of iNO conducted to date, and it confirms a number of prior observations, such as ~~iNO~~ iNO's being rapidly acting, selective for the pulmonary vasculature, and well-tolerated in most patients.

[0068] It is also acknowledged that rapidly decreasing the PVR may be undesirable and even dangerous in patients with concomitant LVD. In the INOT22 study, the overall numbers of SAEs and fatal SAEs are within the expected range for patients with this degree of cardiopulmonary disease. The overall rate is 7/124 (5.6%), which is closely comparable to the rate of 6% recently reported in a very similar cohort of patients. (Taylor CJ et al., 2007, Risk of cardiac catheterization under anaesthesia in children with pulmonary hypertension, *Br J Anaesth* 98(5):657-61). Thus, the overall rate of SAEs would seem to be more closely related to the underlying severity of illness of the patients rather than to the treatments given during this study.

[0069] The INOT22 study results demonstrate that patients who had pre-existing LVD may experience an increased rate of SAEs (e.g., pulmonary edema). During the course of the study, the protocol was amended to exclude patients with a PCWP > 20 mmHg. The benefit/risk of using iNO in patients with clinically significant LVD should be evaluated on a case by case

basis. A reduction in left ventricular afterload may perhaps be applied to minimize the occurrence of pulmonary edema.

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.

BACKGROUND OF THE INVENTION

[0003] INOmax®, (nitric oxide) for inhalation is an approved drug product for the treatment of term and near-term (>34 weeks gestation) neonates having hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension.

[0004] The use of inhaled NO (iNO) has been studied and reported in the literature. (Kieler-Jensen M et al., 1994, Inhaled Nitric Oxide in the Evaluation of Heart Transplant Candidates with Elevated Pulmonary Vascular Resistance, *J Heart Lung Transplantation* 13:366-375; Pearl RG et al., 1983, Acute Hemodynamic Effects of Nitroglycerin in Pulmonary Hypertension, *American College of Physicians* 99:9-13; Ajami GH et al., 2007, Comparison of the Effectiveness of Oral Sildenafil Versus Oxygen Administration as a Test for Feasibility of Operation for Patients with Secondary Pulmonary Arterial Hypertension, *Pediatr Cardiol*; Schulze-Neick I et al., 2003, Intravenous Sildenafil Is a Potent Pulmonary Vasodilator in Children With Congenital Heart Disease, *Circulation* 108(Suppl II):II-167-II-173; Lepore JJ et al., 2002, Effect of Sildenafil on the Acute Pulmonary Vasodilator Response to Inhaled Nitric Oxide in Adults with Primary Pulmonary Hypertension, *The American Journal of Cardiology* 90:677-680; and Ziegler JW et al., 1998, Effects of Dipyridamole and Inhaled Nitric Oxide in Pediatric Patients with Pulmonary Hypertension, *American Journal of Respiratory and Critical Care Medicine* 158:1388-95).

SUMMARY OF THE INVENTION

[0005] One aspect of the invention relates to a pre-screening methodology or protocol having exclusionary criteria to be evaluated by a medical provider prior to treatment of a patient with iNO. One objective of the invention is to evaluate and possibly exclude from treatment patients eligible for treatment with iNO, who have pre-existing left ventricular dysfunction (LVD). Patients who have pre-existing LVD may experience, and are at risk of, an increased rate of adverse events or serious adverse events (e.g., pulmonary edema) when treated with iNO. Such patients may be characterized as having a pulmonary capillary wedge pressure (PCWP) greater than 20 mm Hg, and should be evaluated on a case-by-case basis with respect to the benefit versus risk of using iNO as a treatment option.

[0006] Accordingly, one aspect of the invention includes a method of reducing the risk or preventing the occurrence, in a human patient, of an adverse event (AE) or a serious adverse event (SAE) associated with a medical treatment comprising inhalation of nitric oxide, said method comprising the steps or acts of (a) providing pharmaceutically acceptable nitric oxide gas to a medical provider; and (b) informing the medical provider that excluding human patients who have pre-existing left ventricular dysfunction from said treatment reduces the risk or prevents the occurrence of the adverse event or the serious adverse event associated with said medical treatment.

[0007] Further provided herein is a method of reducing the risk or preventing the occurrence, in a human patient, of an adverse event or a serious adverse event associated with a medical treatment comprising inhalation of nitric oxide, said method comprising the steps or acts of (a) providing pharmaceutically acceptable nitric oxide gas to a medical provider; and (b) informing the medical provider that human patients having pre-existing left ventricular dysfunction experience an increased risk of serious adverse events associated with said medical treatment.

[0008] Another aspect of the invention is a method of reducing one or more of an AE or a SAE in an intended patient population in need of being treated with iNO comprising the steps or acts of (a) identifying a patient eligible for iNO treatment; (b) evaluating and screening the patient to identify if the patient has pre-existing LVD, and (c) excluding from iNO treatment a patient identified as having pre-existing LVD.

[0009] Another aspect of the invention is a method of reducing the risk or preventing the occurrence, in a patient, of one or more of an AE or a SAE associated with a medical treatment comprising iNO, the method comprising the steps or acts of (a) identifying a patient in need of receiving iNO treatment; (b) evaluating and screening the patient to identify if the patient has pre-existing LVD; and (c) administering iNO if the patient does not have pre-existing LVD, thereby reducing the risk or preventing the occurrence of the AE or the SAE associated with the iNO treatment. Alternatively, step (c) may comprise further evaluating the risk versus benefit of utilizing iNO in a patient where the patient has clinically significant LVD before administering iNO to the patient.

[0010] In an exemplary embodiment of the method, the method further comprises informing the medical provider that there is a risk associated with using inhaled nitric oxide in

human patients who have preexisting or clinically significant left ventricular dysfunction and that such risk should be evaluated on a case by case basis.

[0011] In another exemplary embodiment of the method, the method further comprises informing the medical provider that there is a risk associated with using inhaled nitric oxide in human patients who have left ventricular dysfunction.

[0012] In an exemplary embodiment of the methods described herein, a patient having pre-existing LVD is characterized as having PCWP greater than 20 mm Hg.

[0013] In an exemplary embodiment of the method, the patients having pre-existing LVD demonstrate a PCWP $\geq$ 20 mm Hg.

[0014] In another exemplary embodiment of the method, the iNO treatment further comprises inhalation of oxygen (O_2) or concurrent ventilation.

[0015] In another exemplary embodiment of the method, the patients having pre-existing LVD have one or more of diastolic dysfunction, hypertensive cardiomyopathy, systolic dysfunction, ischemic cardiomyopathy, viral cardiomyopathy, idiopathic cardiomyopathy, autoimmune disease related cardiomyopathy, drug-related cardiomyopathy, toxin-related cardiomyopathy, structural heart disease, valvular heart disease, congenital heart disease, or associations thereof.

[0016] In another exemplary embodiment of the method, the patient population comprises children.

[0017] In another exemplary embodiment of the method, the patient population comprises adults.

[0018] In another exemplary embodiment of the method, the patients who have pre-existing LVD are at risk of experiencing an increased rate of one or more AEs or SAEs selected from pulmonary edema, hypotension, cardiac arrest, electrocardiogram changes, hypoxemia, hypoxia, bradycardia or associations thereof.

[0019] In another exemplary embodiment of the method, the intended patient population in need of being treated with inhalation of nitric oxide has one or more of idiopathic pulmonary arterial hypertension characterized by a mean pulmonary artery pressure (PAPm) > 25 mm Hg at rest, PCWP $\leq$ 15 mm Hg, and a pulmonary vascular resistance index (PVRI) > 3 u·m^2; congenital heart disease with pulmonary hypertension repaired and unrepaired characterized by PAPm > 25 mm Hg at rest and PVRI > 3 u·m^2; cardiomyopathy characterized by PAPm > 25

mm Hg at rest and PVRI > 3 u·m^2; or the patient is scheduled to undergo right heart catheterization to assess pulmonary vasoreactivity by acute pulmonary vasodilatation testing.

[0020] In another exemplary embodiment of any of the above methods, the method further comprises reducing left ventricular afterload to minimize or reduce the risk of the occurrence of an adverse event or serious adverse event being pulmonary edema in the patient. The left ventricular afterload may be minimized or reduced by administering a pharmaceutical dosage form comprising nitroglycerin or calcium channel blocker to the patient. The left ventricular afterload may also be minimized or reduced using an intra-aortic balloon pump.

DETAILED DESCRIPTION OF THE EXEMPLARY EMBODIMENTS

[0021] INOmax® (nitric oxide) for inhalation was approved for sale in the United States by the U.S. Food and Drug Administration ("FDA") in 1999. Nitric oxide, the active substance in INOmax®, is a selective pulmonary vasodilator that increases the partial pressure of arterial oxygen (PaO_2) by dilating pulmonary vessels in better ventilated areas of the lung, redistributing pulmonary blood flow away from the lung regions with low ventilation/perfusion (V/Q) ratios toward regions with normal ratios. INOmax® significantly improves oxygenation, reduces the need for extracorporeal oxygenation and is indicated to be used in conjunction with ventilatory support and other appropriate agents. The FDA-approved prescribing information for INOmax® in effect in 2009 is incorporated herein by reference in its entirety. The DOSAGE section of the prescribing information for INOmax® states that the recommended dose of INOmax® is 20 ppm, and that treatment should be maintained up to 14 days or until the underlying oxygen desaturation has resolved and the neonate is ready to be weaned from INOmax® therapy. The ADMINISTRATION section of the prescribing information says that the safety and effectiveness of inhaled nitric oxide have been established in a population receiving other therapies for hypoxic respiratory failure, including vasodilators, intravenous fluids, bicarbonate therapy, and mechanical ventilation. The CONTRAINDICATIONS section of the prescribing information states that INOmax® should not be used in the treatment of neonates known to be dependent on right-to-left shunting of blood.

[0022] INOmax® is a gaseous blend of NO and nitrogen (0.08% and 99.92% respectively for 800 ppm; and 0.01% and 99.99% respectively for 100 ppm) and is supplied in aluminium cylinders as a compressed gas under high pressure. In general, INOmax® is

administered to a patient in conjunction with ventilatory support and O_2. Delivery devices suitable for the safe and effective delivery of gaseous NO for inhalation include the INOvent®, INOmax DS®, INOpulse®, INOblender®, or other suitable drug delivery and regulation devices or components incorporated therein, or other related processes, which are described in various patent documents including USPNs 5,558,083; 5,732,693; 5,752,504; 5,732,694; 6,089,229; 6,109,260; 6,125,846; 6,164,276; 6,581,592; 5,918,596; 5,839,433; 7,114,510; 5,417;950; 5,670,125; 5,670,127; 5,692,495; 5,514,204; 7,523,752; 5,699,790; 5,885,621; US Patent Application Serial Nos. 11/355,670 (US 2007/0190184); 10/520,270 (US 2006/0093681); 11/401,722 (US 2007/0202083); 10/053,535 (US 2002/0155166); 10/367,277 (US 2003/0219496); 10/439,632 (US 2004/0052866); 10/371,666 (US 2003/0219497); 10/413,817 (US 2004/0005367); 12/050,826 (US 2008/0167609); and PCT/US2009/045266, all of which are incorporated herein by reference in their entirety.

[0023] Such devices deliver INOmax® into the inspiratory limb of the patient breathing circuit in a way that provides a constant concentration of NO to the patient throughout the inspired breath. Importantly, suitable delivery devices provide continuous integrated monitoring of inspired O_2, NO_2 and NO, a comprehensive alarm system, a suitable power source for uninterrupted NO delivery, and a backup NO delivery capability.

[0024] As used herein, the term "children" (and variations thereof) includes those being around 4 weeks to 18 years of age.

[0025] As used herein, the term "adult" (and variations thereof) includes those being over 18 years of age.

[0026] As used herein, the terms "adverse event" and "AE" (and variations thereof) mean any untoward occurrence in a subject or clinical investigation subject administered a pharmaceutical product (such as nitric oxide) and which does not necessarily have a causal relationship with such treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporarily associated with the use of a medicinal/investigational product, whether or not related to the investigational product. A relationship to the investigational product is not necessarily proven or implied. However, abnormal values are not reported as adverse events unless considered clinically significant by the investigator.

[0027] As used herein, the terms "adverse drug reaction" and "ADR" (and variations thereof) mean any noxious and unintended response to a medicinal product related to any dose.

[0028] As used herein, the terms "serious adverse event" and "SAE" (or "serious adverse drug reaction" and "serious ADR") (and variations thereof) mean a significant hazard or side effect, regardless of the investigator's opinion on the relationship to the investigational product. A serious adverse event or reaction is any untoward medical occurrence that at any dose: results in death; is life-threatening (which refers to an event/reaction where the patient was at risk of death at the time of the event/reaction, however this does not refer to an event/reaction that hypothetically may have caused death if it were more severe); requires inpatient hospitalization or results in prolongation of existing hospitalization; results in persistent or significant disability/incapacity; is a congenital anomaly/birth defect; or is a medically important event or reaction. Medical and scientific judgment is exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed above--these are also considered serious. Examples of such medical events include cancer, allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in hospitalizations, or the development of drug dependency or drug abuse. Serious clinical laboratory abnormalities directly associated with relevant clinical signs or symptoms are also reported.

[0029] Left Ventricular Dysfunction. Patients having pre-existing LVD may be described in general as those with elevated pulmonary capillary wedge pressure, including those with diastolic dysfunction (including hypertensive cardiomyopathy), those with systolic dysfunction, including those with cardiomyopathies (including ischemic or viral cardiomyopathy, or idiopathic cardiomyopathy, or autoimmune disease related cardiomyopathy, and side effects due to drug related or toxic-related cardiomyopathy), or structural heart disease, valvular heart disease, congenital heart disease, idiopathic pulmonary arterial hypertension, pulmonary hypertension and cardiomyopathy, or associations thereof. Identifying patients with pre-existing LVD is known to those skilled in the medicinal arts, and such techniques for example may include assessment of clinical signs and symptoms of heart failure, or echocardiography diagnostic screening.

[0030] Pulmonary Capillary Wedge Pressure. Pulmonary capillary wedge pressure, or "PCWP", provides an estimate of left atrial pressure. Identifying patients with pre-existing PCWP is known to those skilled in the medicinal arts, and such techniques for example may include measuring by inserting balloon-tipped, multi-lumen catheter (also known as a Swan-Ganz catheter). Measurement of PCWP may be used as a means to diagnose the severity of LVD (sometimes also referred to as left ventricular failure). PCWP is also a desired measure when evaluating pulmonary hypertension. Pulmonary hypertension is often caused by an increase in pulmonary vascular resistance (PVR), but may also arise from increases in pulmonary venous pressure and pulmonary blood volume secondary to left ventricular failure or mitral or aortic valve disease.

[0031] In cardiac physiology, the term "afterload" is used to mean the tension produced by a chamber of the heart in order to contract. If the chamber is not mentioned, it is usually assumed to be the left ventricle. However, the strict definition of the term relates to the properties of a single cardiac myocyte. It is therefore of direct relevance only in the laboratory; in the clinic, the term end-systolic pressure is usually more appropriate, although not equivalent.

[0032] The term "left ventricular afterload" (and variations thereof) refers to the pressure that the chamber of the heart has to generate in order to eject blood out of the chamber. Thus, it is a consequence of the aortic pressure, since the pressure in the ventricle must be greater than the systemic pressure in order to open the aortic valve. Everything else held equal, as afterload increases, cardiac output decreases. Disease processes that increase the left ventricular afterload include increased blood pressure and aortic valve disease. Hypertension (increased blood pressure) increases the left ventricular afterload because the left ventricle has to work harder to eject blood into the aorta. This is because the aortic valve won't open until the pressure generated in the left ventricle is higher than the elevated blood pressure. Aortic stenosis increases the afterload because the left ventricle has to overcome the pressure gradient caused by the stenotic aortic valve in addition to the blood pressure in order to eject blood into the aorta. For instance, if the blood pressure is 120/80, and the aortic valve stenosis creates a trans-valvular gradient of 30 mmHg, the left ventricle has to generate a pressure of 110 mmHg in order to open the aortic valve and eject blood into the aorta. Aortic insufficiency increases afterload because a percentage of the blood that is ejected forward regurgitates back through the diseased aortic valve. This leads to elevated systolic blood pressure. The diastolic blood

pressure would fall, due to regurgitation. This would result in an increased pulse pressure. Mitral regurgitation decreases the afterload. During ventricular systole, the blood can regurgitate through the diseased mitral valve as well as be ejected through the aortic valve. This means that the left ventricle has to work less to eject blood, causing a decreased afterload. Afterload is largely dependent upon aortic pressure.

[0033] An intra-aortic balloon pump (IABP) is a mechanical device that is used to decrease myocardial oxygen demand while at the same time increasing cardiac output. By increasing cardiac output it also increases coronary blood flow and therefore myocardial oxygen delivery. It consists of a cylindrical balloon that sits in the aorta and counterpulsates. That is, it actively deflates in systole, increasing forward blood flow by reducing afterload ~~thus~~, and actively inflates in diastole, increasing blood flow to the coronary arteries. These actions have the combined result of decreasing myocardial oxygen demand and increasing myocardial oxygen supply. The balloon is inflated during diastole by a computer controlled mechanism, usually linked to either an ECG or a pressure transducer at the distal tip of the catheter; some IABPs, such as the Datascope System 98XT, allow for asynchronous counterpulsation at a set rate, though this setting is rarely used. The computer controls the flow of helium from a cylinder into and out of the balloon. Helium is used because its low viscosity allows it to travel quickly through the long connecting tubes, and it has a lower risk of causing a harmful embolism should the balloon rupture while in use. Intraaortic balloon counterpulsation is used in situations when the heart's own cardiac output is insufficient to meet the oxygenation demands of the body. These situations could include cardiogenic shock, severe septic shock, post cardiac surgery and numerous other situations.

[0034] Patients eligible for treatment with iNO. In general, patients approved for treatment of iNO are term and near-term (>34 weeks gestation) neonates having hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension, a condition also known as persistent pulmonary hypertension in the newborn (PPHN). Due to the selective, non-systemic nature of iNO to reduce pulmonary hypertension, physicians skilled in the art further employ INOmax® to treat or prevent pulmonary hypertension and improve blood O_2 levels in a variety of other clinical settings, including in both pediatric and adult patients suffering from acute respiratory distress syndrome (ARDS), pediatric and adult patients undergoing cardiac or transplant surgeries, pediatric and adult

patients for testing to diagnose reversible pulmonary hypertension, and in pediatric patients with congenital diaphragmatic hernia. In most, if not all, of these applications, INOmax® acts by preventing or treating reversible pulmonary vasoconstriction, reducing pulmonary arterial pressure and improving pulmonary gas exchange.

[0035] A small proportion of INOmax® sales stem from its use by clinicians in a premature infant population. In these patients, INOmax® is generally utilized by physicians as a rescue therapy primarily to vasodilate the lungs and improve pulmonary gas exchange. Some physicians speculate that INOmax® therapy may promote lung development and/or reduce or prevent the future development of lung disease in a subset of these patients. Although the precise mechanism(s) responsible for the benefits of INOmax® therapy in these patients is not completely understood, it appears that the benefits achieved in at least a majority of these patients are due to the ability of INOmax® to treat or prevent reversible pulmonary vasoconstriction.

[0036] In clinical practice, the use of INOmax® has reduced or eliminated the use of high risk systemic vasodilators for the treatment of PPHN. INOmax®, in contrast to systemic vasodilators, specifically dilates the pulmonary vasculature without dilating systemic blood vessels. Further, iNO preferentially vasodilates vessels of aveoli that are aerated, thus improving V/Q matching. In contrast, systemic vasodilators may increase blood flow to atelectatic (deflated or collapsed) alveoli, thereby increasing V/Q mismatch and worsening arterial oxygenation. (*See* Rubin LJ, Kerr KM, Pulmonary Hypertension, in *Critical Care Medicine: Principles of Diagnosis and Management in the Adult*, *2d Ed.*, Parillo JE, Dellinger RP (eds.), Mosby, Inc. 2001, pp. 900-09 at 906; Kinsella JP, Abman SH, The Role of Inhaled Nitric Oxide in Persistent Pulmonary Hypertension of the Newborn, in *Acute Respiratory Care of the Neonate: A Self-Study Course*, *2d Ed.*, Askin DF (ed.), NICU Ink Book Publishers, 1997, pp. 369-378 at 372-73).

[0037] INOmax® also possesses highly desirable pharmacokinetic properties as a lung-specific vasodilator when compared to other ostensibly "pulmonary-specific vasodilators." For example, the short half-life of INOmax® allows INOmax® to exhibit rapid "on" and "off" responses relative to INOmax® dosing, in contrast to non-gaseous alternatives. In this way, INOmax® can provide physicians with a useful therapeutic tool to easily control the magnitude

and duration of the pulmonary vasodilatation desired. Also, the nearly instantaneous inactivation of INOmax® in the blood significantly reduces or prevents vasodilatation of non-pulmonary vessels.

[0038] The pivotal trials leading to the approval of INOmax® were the CINRGI and NINOS study.

[0039] CINRGI study. (See Davidson et al., March 1998, 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, No. 3, p. 325).

[0040] This study was a double-blind, randomized, placebo-controlled, multicenter trial of 186 term and near-term neonates with pulmonary hypertension and hypoxic respiratory failure. The primary objective of the study was to determine whether INOmax® would reduce the receipt of extracorporeal membrane oxygenation (ECMO) in these patients. Hypoxic respiratory failure was caused by meconium aspiration syndrome (MAS) (35%), idiopathic persistent pulmonary hypertension of the newborn (PPHN) (30%), pneumonia/sepsis (24%), or respiratory distress syndrome (RDS) (8%). Patients with a mean PaO_2 of 54 mm Hg and a mean oxygenation index (OI) of 44 cm H_2O/mm Hg were randomly assigned to receive either 20 ppm INOmax® (n=97) or nitrogen gas (placebo; n=89) in addition to their ventilatory support. Patients that exhibited a $PaO_2 > 60$ mm Hg and a pH < 7.55 were weaned to 5 ppm INOmax® or placebo. The primary results from the CINRGI study are presented in Table 1. ECMO was the primary endpoint of the study.

Table 1: Summary of Clinical Results from CINRGI Study

	Placebo	**INOmax®**	**P value**
Death or ECMO	51/89 (57%)	30/97 (31%)	<0.001

	Placebo	INOmax®	P value
Death	5/89 (6%)	3/97 (3%)	0.48

[0041] Significantly fewer neonates in the ECMO group required ECMO, and INOmax® significantly improved oxygenation, as measured by PaO_2, OI, and alveolar-arterial gradient.

[0042] NINOS study. (See Inhaled Nitric Oxide in Full-Term and Nearly Full-Term Infants with Hypoxic Respiratory Failure; NEJM, Vol. 336, No. 9, 597).

[0043] The Neonatal Inhaled Nitric Oxide Study (NINOS) group conducted a double-blind, randomized, placebo-controlled, multicenter trial in 235 neonates with hypoxic respiratory failure. The objective of the study was to determine whether iNO would reduce the occurrence of death and/or initiation of ECMO in a prospectively defined cohort of term or near-term neonates with hypoxic respiratory failure unresponsive to conventional therapy. Hypoxic respiratory failure was caused by meconium aspiration syndrome (MAS; 49%), pneumonia/sepsis (21%), idiopathic primary pulmonary hypertension of the newborn (PPHN; 17%), or respiratory distress syndrome (RDS; 11%). Infants ≤ 14 days of age (mean, 1.7 days) with a mean PaO_2 of 46 mm Hg and a mean oxygenation index (OI) of 43 cm H_2O/mmHg were initially randomized to receive 100% O_2 with (n=114) or without (n=121) 20 ppm NO for up to 14 days. Response to study drug was defined as a change from baseline in PaO_2 30 minutes after starting treatment (full response = > 20 mmHg, partial = 10–20 mm Hg, no response = < 10 mm Hg). Neonates with a less than full response were evaluated for a response to 80 ppm NO or control gas. The primary results from the NINOS study are presented in Table 2.

Table 2: Summary of Clinical Results from NINOS Study

	Control (n=121)	NO (n=114)	P value
Death or ECMO*, †	77 (64%)	52 (46%)	0.006
Death	20 (17%)	16 (14%)	0.60
ECMO	66 (55%)	44 (39%)	0.014

* Extracorporeal membrane oxygenation
† Death or need for ECMO was the study's primary end point

[0044] Adverse Events from CINRGI & NINOS. Controlled studies have included 325 patients on INOmax® doses of 5 to 80 ppm and 251 patients on placebo. Total mortality in the pooled trials was 11% on placebo and 9% on INOmax®, a result adequate to exclude INOmax® mortality being more than 40% worse than placebo.

[0045] In both the NINOS and CINRGI studies, the duration of hospitalization was similar in INOmax® and placebo-treated groups.

[0046] From all controlled studies, at least 6 months of follow-up is available for 278 patients who received INOmax® and 212 patients who received placebo. Among these patients, there was no evidence of an AE of treatment on the need for re-hospitalization, special medical services, pulmonary disease, or neurological sequelae.

[0047] In the NINOS study, treatment groups were similar with respect to the incidence and severity of intracranial hemorrhage, Grade IV hemorrhage, per ventricular leukomalacia, cerebral infarction, seizures requiring anticonvulsant therapy, pulmonary hemorrhage, or gastrointestinal hemorrhage.

[0048] The table below shows adverse reactions that occurred in at least 5% of patients receiving INOmax® in the CINRGI study. None of the differences in these adverse reactions were statistically significant when iNO patients were compared to patients receiving placebo.

Table 3: ADVERSE REACTIONS ON THE CINRGI TRIAL

Adverse Reaction	Placebo (n=89)	Inhaled NO (n=97)
Atelectasis	5 (4.8%)	7 (6.5%)
Bilirubinemia	6 (5.8%)	7 (6.5%)
Hypokalemia	5 (4.8%)	9 (8.3%)
Hypotension	3 (2.9%)	6 (5.6%)
Thrombocytopenia	20 (19.2%)	16 (14.8%)

[0049] Post-Marketing Experience. The following AEs have been reported as part of the post-marketing surveillance. These events have not been reported above. Given the nature of spontaneously reported post-marketing surveillance data, it is impossible to determine the actual incidence of the events or definitively establish their causal relationship to the drug. The listing is alphabetical: dose errors associated with the delivery system; headaches associated with environmental exposure of INOmax® in hospital staff; hypotension associated with acute withdrawal of the drug; hypoxemia associated with acute withdrawal of the drug; pulmonary edema in patients with CREST syndrome.

[0050] An analysis of AEs and SAEs from both the CINRGI and NINOS studies, in addition to post-marketing surveillance, did not suggest that patients who have pre-existing LVD could experience an increased risk of AEs or SAEs. Nor was it predictable to physicians skilled in the art that patients having pre-existing LVD (possibly identified as those patients having a PCWP greater than 20 mmHg) should be evaluated in view of the benefit versus risk of using iNO in patients with clinically significant LVD, and that these patients should be evaluated on a case by case basis.

EXAMPLE 1: INOT22 STUDY

[0051] The INOT22 study, 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 vasodilatory testing" was conducted both to assess the safety and

effectiveness of INOmax® as a diagnostic agent in patients undergoing assessment of pulmonary hypertension (primary endpoint), and to confirm the hypothesis that iNO is selective for the pulmonary vasculature (secondary endpoint).

[0052] During, and upon final analysis of the INOT22 study results, applicants discovered that rapidly decreasing the pulmonary vascular resistance, via the administration of iNO to a patient in need of such treatment, may be detrimental to patients with concomitant, pre-existing LVD. Therefore, a precaution for patients with LVD was proposed to be included in amended prescribing information for INOmax®. Physicians were further informed to consider reducing left ventricular afterload to minimize the occurrence of pulmonary edema in patients with pre-existing LVD.

[0053] In particular, the INOT22 protocol studied consecutive children undergoing cardiac catheterization that were prospectively enrolled at 16 centers in the US and Europe. Inclusion criteria: 4 weeks to 18 years of age, pulmonary hypertension diagnosis, i.e. either idiopathic pulmonary hypertension (IPAH) or related to congenital heart disease (CHD) (repaired or unrepaired) or cardiomyopathy, with pulmonary vascular resistance index (PVRI) > 3 u-m^2. Later amendments, as discussed herein, added an additional inclusionary criterion of a PCWP less than 20 mm Hg. Patients were studied under general anaesthesia, or with conscious sedation, according to the practice of the investigator. Exclusion criteria: focal infiltrates on chest X-ray, history of intrinsic lung disease, and/or currently taking PDE-5 inhibitors, prostacyclin analogues or sodium nitroprusside. The study involved supplemental O_2 and NO for inhalation plus O_2 in the evaluation of the reactivity of the pulmonary vasculature during acute pulmonary vasodilator testing. Consecutive children undergoing cardiac catheterization were prospectively enrolled at 16 centers in the US and Europe. As hypotension is expected in these neonatal populations, the comparison between iNO and placebo groups is difficult to assess. A specific secondary endpoint was evaluated in study INOT22 to provide a more definitive evaluation.

[0054] The primary objective was to compare the response frequency with iNO and O_2 vs. O_2 alone; in addition, all subjects were studied with iNO alone. Patients were studied during five periods: Baseline 1, Treatment Period 1, Treatment Period 2, Baseline 2 and Treatment Period 3. All patients received all three treatments; treatment sequence was randomized by

center in blocks of 4; in Period 1, patients received either NO alone or O_2 alone, and the alternate treatment in Period 3. All patients received the iNO and O_2 combination treatment in Period 2. Once the sequence was assigned, treatment was unblinded. Each treatment was given for 10 minutes prior to obtaining hemodynamic measurements, and the Baseline Period 2 was at least 10 minutes.

[0055] Results for the intent-to-treat (ITT) population, defined as all patients who were randomized to receive drug, indicated that treatment with NO plus O_2 and O_2 alone significantly increased systemic vascular resistance index (SVRI) (Table 4). The change from baseline for NO plus O_2 was 1.4 Woods Units per meter^2 (WU·m^2) ($p = 0.007$) and that for O_2 was 1.3 WU·m^2 ($p = 0.004$). While the change from baseline in SVRI with NO alone was -0.2 WU·m^2 ($p = 0.899$) which demonstrates a lack of systemic effect.

Table 4: SVRI Change From Baseline by Treatment (Intent-to-Treat)

	Treatment		
SVRI ($WU \cdot m^2$)	**NO Plus O_2 (n=109)**	**O_2 (n=106)**	**NO (n=106)**
Baseline (room air)			
Mean	17.2	17.6	18.0
Standard Deviation (SD)	8.86	9.22	8.44
Median	15.9	16.1	16.2
Minimum, maximum	-7.6, 55.6	-7.6, 55.6	1.9, 44.8
Post-treatment			
Mean	18.7	18.9	17.8
SD	9.04	8.78	9.40
Median	17.1	17.1	15.4
Minimum, maximum	3.0, 47.4	3.9, 43.6	3.3, 50.7
Change From Baseline			
Mean	1.4	1.3	-0.2
SD	5.94	5.16	4.65
Median	1.2	1.0	0.2
Minimum, maximum	-20.5, 19.1	-18.1, 17.7	-12.5, 12.7
p-value[a]	0.007	0.004	0.899
Pairwise comparisons NO plus O_2 versus O_2, p=0.952 NO plus O_2 versus NO, p=0.014 O_2 versus NO, p=0.017			

[a] p-value from a Wilcoxon Signed Rank Test. Only patients with data to determine response at both treatments are included in this analysis.
Source: INOT22 CSR Table 6.4.1 and Appendix 16.2.6 (ATTACHMENT 1)

[0056] The ideal pulmonary vasodilator should reduce PVRI and/or PAPm while having no appreciable effect on systemic blood pressure or SVRI. In this case, the ratio of PVRI to SVRI would decrease, given some measure of the selectivity of the agent for the pulmonary vascular bed. The change in the ratio of PVRI to SVRI by treatment is shown in Table 5.

Table 5: Change in Ratio of PVRI to SVRI by Treatment (Intent-to-Treat)

	Treatment		
Ratio PVRI/SVRI	**NO Plus O_2 (n=108)**	**O_2 (n=105)**	**NO (n=106)**
Baseline			
Mean	0.6	0.5	0.6
SD	0.60	0.45	0.56
Median	0.5	0.5	0.4
Minimum, Maximum	-1.6, 4.7	-1.6, 1.8	0.0, 4.7
Post Treatment			
Mean	0.4	0.4	0.5
SD	0.31	0.31	0.46
Median	0.3	0.4	0.3
Minimum, Maximum	0.0, 1.3	0.0, 1.4	-1.2, 2.2
Change from Baseline			
Mean	-0.2	-0.1	-0.1
SD	0.52	0.31	0.54
Median	-0.1	-0.1	0.0
Minimum, Maximum	-4.4, 2.0	-1.6, 2.0	-4.4, 1.6
P Value[1]	< 0.001	< 0.001	0.002

[1] Wilcoxon Signed Rank Test
Source: INOT22 CSR Table 6.5.1 (ATTACHMENT 2)

[0057] All three treatments have a preferential effect on the pulmonary vascular bed, suggesting that all three are selective pulmonary vasodilators. The greatest reduction in the ratio was during treatment with NO plus O_2, possibly due to the decrease in SVRI effects seen with O_2 and NO plus O_2. These results are displayed as percent change in the ratio (See Table 6).

Table 6: Percent Change in Ratio of PVRI to SVRI by Treatment (Intent-to-Treat)

	Treatment		
Ratio PVRI/SVRI	**NO Plus O_2 (n=108)**	**O_2 (n=105)**	**NO (n=106)**
Baseline			
Mean	0.6	0.5	0.6
SD	0.60	0.45	0.56
Median	0.5	0.5	0.4
Minimum, Maximum	-1.6, 4.7	-1.6, 1.8	0.0, 4.7
Post Treatment			
Mean	0.4	0.4	0.5
SD	0.31	0.31	0.46
Median	0.3	0.4	0.3
Minimum, Maximum	0.0, 1.3	0.0, 1.4	-1.2, 2.2
Percent Change from Baseline			
Mean	-33.5	-19.3	-6.2
SD	36.11	34.59	64.04
Median	-34.0	-21.3	-13.8
Minimum, Maximum	-122.2, 140.1	-122.7, 93.3	-256.1, 294.1
P Value[1]	< 0.001	< 0.001	0.006

[1] Wilcoxon Signed Rank Test
Source: INOT22 CSR Table 6.5.2 (ATTACHMENT 3)

[0058] NO plus O_2 appeared to provide the greatest reduction in the ratio, suggesting that NO plus O_2 was more selective for the pulmonary vasculature than either agent alone.

[0059] Overview of Cardiovascular Safety. In the INOT22 diagnostic study, all treatments (NO plus O_2, O_2, and NO) were well-tolerated. Seven patients of 134 treated experienced an AE during the study. These included cardiac arrest, bradycardia, low cardiac output (CO) syndrome, elevated ST segment (the portion of an electrocardiogram between the end of the QRS complex and the beginning of the T wave) on the electrocardiography (ECG)

decreased O_2 saturation, hypotension, mouth hemorrhage and pulmonary hypertension (PH). The numbers of patients and events were too small to determine whether risk for AEs differed by treatment, diagnosis, age, gender or race. Eight patients are shown in Table 5 due to the time period in which events are reported. AEs were reported for 12 hours or until hospital discharge (which limits the period in which such events can be reported). There is technically no time limit in which SAEs are to be reported. So, there were 7 AEs during the study and at least one SAE after the study.

[0060] A total of 4 patients had AEs assessed as being related to study drug. These events included bradycardia, low CO syndrome, ST segment elevation on the ECG, low O_2 saturation, PH and hypotension. All but 2 AEs were mild or moderate in intensity and were resolved. Study treatments had slight and non-clinically significant effects on vital signs including heart rate, systolic arterial pressure and diastolic arterial pressure. When an investigator records an AE, they are required to say if (in their opinion) the event is related to the treatment or not. In this case, 4 of 7 were considered by the investigator to be related to treatment.

[0061] The upper limit of normal PCWP in children is 10-12 mm Hg and 15 mm Hg in adults. In INOT22, a baseline PCWP value was not included as exclusion criteria. However, after the surprising and unexpected identification of SAEs in the early tested patients, it was determined that patients with pre-existing LVD had an increased risk of experiencing an AE or SAE upon administration (e.g., worsening of left ventricular function due to the increased flow of blood through the lungs). Accordingly, the protocol for INOT22 was thereafter amended to exclude patients with a baseline PCWP greater than 20 mm Hg after one patient experienced acute circulatory collapse and died during the study. The value "20 mm Hg" was selected to avoid enrollment of a pediatric population with LVD such that they would be most likely at-risk for these SAEs.

[0062] SAEs were collected from the start of study treatment until hospital discharge or 12 hours, whichever occurred sooner. Three SAEs were reported during the study period, and a total of 7 SAEs were reported. Three of these were fatal SAEs and 4 were nonfatal (one of which led to study discontinuation). In addition, one non-serious AE also led to

discontinuation. A list of subjects who died, discontinued or experienced an SAE is provided in Table 7 below.

Table 7: Subjects that died, discontinued or experienced SAEs

Patient number	AE	Serious?	Fatal?	Discontinued treatment?
01020	Desaturation (hypoxia)	No	No	Yes
02002	Pulmonary edema	Yes	No	No
04001	Hypotension and cardiac arrest	Yes	Yes	No
04003	Hypotension and ECG changes	Yes	No	Yes
04008	Hypotension and hypoxemia	Yes	Yes	No
05002	Hypoxia and bradycardia (also pulmonary edema)	Yes	Yes	No
07003	Cardiac arrest	Yes	No	No
17001	Hypoxia	Yes	No	No

[0063] Two of the 3 fatal SAEs were deemed related to therapy. All 4 non-fatal SAEs were also considered related to therapy. The numbers of patients and events were too small to determine whether risk for SAEs differed by treatment, diagnosis, age, gender or race. At least two patients developed signs of pulmonary edema (subjects 05002 and 02002). This is of interest because pulmonary edema has previously been reported with the use of iNO in patients with LVD, and may be related to decreasing PVRI and overfilling of the left atrium. (Hayward CS et al., 1996, Inhaled Nitric Oxide in Cardiac Failure: Vascular Versus Ventricular Effects, *J Cardiovascular Pharmacology* 27:80-85; Bocchi EA et al., 1994, Inhaled Nitric Oxide Leading to Pulmonary Edema in Stable Severe Heart Failure, *Am J Cardiology* 74:70-72; and, Semigran MJ et al., 1994, Hemodynamic Effects of Inhaled Nitric Oxide in Heart Failure, *J Am Coll Cardiology* 24:982-988).

[0064] Although the SAE rate is within range for this population, it appears that patients with the most elevated PCWP at baseline had a disproportionately high number of these events. (Bocchi EA et al., 1994; Semigran MJ et al., 1994).

[0065] In the INOT22 study, 10 of the total 134 patients had a baseline PCWP $\geq$ 18 mm Hg (7.5%), of which 3 subjects (04001, 02002 and 04003) had a SAE or were prematurely discontinued from the study (30%), compared to 6.5% for the entire cohort.

[0066] Although there were very few significant AEs in the INOT22 study, these events are consistent with the expected physiologic changes in patients with severe LVD. The events also corroborate prior observations that iNO is rapidly acting, selective for the pulmonary vasculature, and well-tolerated in most patients. The actual incidence of acute LVD during acute ventricular failure (AVT) is unknown. However, it is reasonable to expect that a significant number of patients are at-risk for an increased incidence of SAEs upon iNO treatment based upon the nature of the underlying nature of the illness, i.e., pulmonary hypertension and cardiovascular disease more generally. Thus, it would be advantageous to have physicians identify these patients prior to beginning iNO treatment, so that the physicians are alerted to this possible outcome.

[0067] Benefits and Risks Conclusions. The INOT22 study was designed to demonstrate the physiologic effects of iNO in a well defined cohort of children (i.e., intended patient population) with pulmonary hypertension using a high concentration, 80 ppm, of iNO, i.e., one that would be expected to have the maximal pharmacodynamic effect. INOT22 was the largest and most rigorous pharmacodynamic study of iNO conducted to date, and it confirms a number of prior observations, such as iNO's being rapidly acting, selective for the pulmonary vasculature, and well-tolerated in most patients.

[0068] It is also acknowledged that rapidly decreasing the PVR may be undesirable and even dangerous in patients with concomitant LVD. In the INOT22 study, the overall numbers of SAEs and fatal SAEs are within the expected range for patients with this degree of cardiopulmonary disease. The overall rate is 7/124 (5.6%), which is closely comparable to the rate of 6% recently reported in a very similar cohort of patients. (Taylor CJ et al., 2007, Risk of cardiac catheterization under anaesthesia in children with pulmonary hypertension, *Br J Anaesth* 98(5):657-61). Thus, the overall rate of SAEs would seem to be more closely related to the underlying severity of illness of the patients rather than to the treatments given during this study.

[0069] The INOT22 study results demonstrate that patients who had pre-existing LVD may experience an increased rate of SAEs (e.g., pulmonary edema). During the course of the study, the protocol was amended to exclude patients with a PCWP > 20 mmHg. The benefit/risk of using iNO in patients with clinically significant LVD should be evaluated on a case by case

basis. A reduction in left ventricular afterload may perhaps be applied to minimize the occurrence of pulmonary edema.

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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 14/454,373	Filing Date 08/07/2014	☐ To be Mailed

ENTITY: ☐ LARGE ☒ SMALL ☐ MICRO

APPLICATION AS FILED – PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).			
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))				
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT **08/13/2014**

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	* 30	Minus	** 30	= 0	X $40 =	0
Independent (37 CFR 1.16(h))	* 4	Minus	***4	= 0	X $210 =	0
☐ Application Size Fee (37 CFR 1.16(s))						
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
					TOTAL ADD'L FEE	**0**

AMENDMENT

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =	
Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =	
☐ Application Size Fee (37 CFR 1.16(s))						
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
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	Attorney Docket Number	26047-0003011

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	Art Unit	
	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)	2014-08-08
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.**

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.

Electronic Acknowledgement Receipt

EFS ID:	19820616
Application Number:	14454373
International Application Number:	
Confirmation Number:	3860
Title of Invention:	Methods of Treating Term and Near-Term Neonates Having Hypoxic Respiratory Failure Associated with Clinical or Echocardiographic Evidence of Pulmonary Hypertension
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:	08-AUG-2014
Filing Date:	
Time Stamp:	17:21:07
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	Transmittal Letter	IDS.pdf	62554 ba207e52261bff433c230efd9e6a371518e8d73b	no	1

Warnings:	
Information:	

2	Information Disclosure Statement (IDS) Form (SB08)	SB08.pdf	615442 d5cf7403b8b8980e728df271fab73abe0aaeedf4	no	8

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.

Total Files Size (in bytes):	677996

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	Conf. No. :	3860
Serial No.	:	14/454,373		
Filed	:	August 7, 2014		
Title	:	METHODS FOR TREATING PATIENTS WHO ARE CANDIDATES FOR INHALED NITRIC OXIDE TREATMENT		

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

SECOND INFORMATION DISCLOSURE STATEMENT

Please consider the references listed on the enclosed PTO-SB-08 Form. Under 35 USC §120, this application relies on the earlier filing date of application serial numbers 12/494,598, filed on June 30, 2009; 12/820,866, filed on June 22, 2010; 12/821,041, filed on June 22, 2010; 13/651,660, filed on October 15, 2012; 13/683,417, filed on November 21, 2012; 13/683,444, filed on November 21, 2012; and 14/451,057, filed on August 4, 2014. The cited references were submitted to and/or cited by the Office in the prior applications and therefore are not provided in this application.

This statement is being filed within three months of the filing date of the application. Apply any necessary charges or credits to Deposit Account 06-1050, referencing the above attorney docket number.

Respectfully submitted,

Date: August 8, 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

23274197.doc

FISH.
FISH & RICHARDSON

Street Address
Fish & Richardson P.C.
One Marina Park Drive
Boston, MA 02210-1878

Mail Address
P.O. Box 1022
Minneapolis, MN 55440-1022

617 542 5070 main
877 769 7945 fax

August 7, 2014

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

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

Presented for filing is a new continuation patent application for prioritized examination of:

Inventor: JAMES S. BALDASSARRE

Title: METHODS OF TREATING TERM AND NEAR-TERM NEONATES HAVING HYPOXIC RESPIRATORY FAILURE ASSOCIATED WITH CLINICAL OR ECHOCARDIOGRAPHIC EVIDENCE OF PULMONARY HYPERTENSION

This application claims the benefit of priority to the following applications:

Application No.	Country	Filing Date (MM/DD/YYYY)
12/494,598	United States	06/30/2009
12/820,866	United States	06/22/2010
12/821,041	United States	06/22/2010
13/651,660	United States	10/15/2012
13/683,417	United States	11/21/2012
13/683,444	United States	11/21/2012
14/451,057	United States	08/04/2014

Enclosed are the following papers, including those required to receive a filing date under 37 C.F.R. § 1.53(b):

	Pages
Specification	22
Claims	6
Abstract	1
Declaration (with cover page)	2

FISH.
FISH & RICHARDSON

Commissioner for Patents
August 7, 2014

Enclosures:

— Application Data Sheet, 8 pages.
— New disclosure information, including:
SB-08 (10 pages);
Information Disclosure Statement (2 pages)
— Power of Attorney, 3 pages.
— Certification and Request for Prioritized Examination (Track I), 1 page

Applicant claims small entity status. See 37 CFR 1.27.

Basic Filing Fee			$70
Search Fee			$300
Examination Fee			$360
Publication fee			$0
Track I processing fee			$70
Track I prioritized examination fee			$2000
Total Claims 20	over 20	**0 x $80**	$0
Independent Claims 3	over 3	**0 x $420**	$0
Fee for Multiple Dependent claims			$0
Application size fee for each 50 pages over 100 Total Sheets: 42x .75 - 100/50 = 0x			$0
Total Filing fee			$2800

The filing fee totaling $2800 is being paid on the Electronic Filing System (EFS) by way of Deposit Account authorization.

If this application is found to be incomplete, or if a telephone conference would otherwise be helpful, please call the undersigned at (617) 542-5070.

FISH.
FISH & RICHARDSON

Commissioner for Patents
August 7, 2014

Direct all correspondence to the following:

94169
PTO Customer Number

Respectfully submitted,

/Janis K. Fraser/

Janis K. Fraser, Ph.D., J.D.

Reg. No. 34,819
Enclosures
JKF/cng
23270585.doc

PTO/AIA/14 (12-13)
Approved for use through 01/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	26047-0003011
	Application Number	
Title of Invention	Methods of Treating Term and Near-Term Neonates Having Hypoxic Respiratory Failure Associated with Clinical or Echocardiographic Evidence of Pulmonary Hypertension	

The application data sheet is part of the provisional or nonprovisional application for which it is being submitted. The following form contains the bibliographic data arranged in a format specified by the United States Patent and Trademark Office as outlined in 37 CFR 1.76.
This document may be completed electronically and submitted to the Office in electronic format using the Electronic Filing System (EFS) or the document may be printed and included in a paper filed application.

Secrecy Order 37 CFR 5.2

☐ Portions or all of the application associated with this Application Data Sheet may fall under a Secrecy Order pursuant to 37 CFR 5.2 (Paper filers only. Applications that fall under Secrecy Order may not be filed electronically.)

Inventor Information:

Inventor 1 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	James	S.	Baldassarre	

Residence Information (Select One) ◉ US Residency ○ Non US Residency ○ Active US Military Service

City	Doylestown	State/Province	PA	Country of Residence i	US

Mailing Address of Inventor:

Address 1	145 Pebble Woods Drive		
Address 2			
City	Doylestown	State/Province	PA
Postal Code	18901	Country i	US

All Inventors Must Be Listed - Additional Inventor Information blocks may be generated within this form by selecting the **Add** button. Add

Correspondence Information:

Enter either Customer Number or complete the Correspondence Information section below.
For further information see 37 CFR 1.33(a).

☐ **An Address is being provided for the correspondence Information of this application.**

Customer Number	94169		
Email Address	apsi@fr.com	Add Email	Remove Email

Application Information:

Title of the Invention	Methods of Treating Term and Near-Term Neonates Having Hypoxic Respiratory Failure Associated with Clinical or Echocardiographic Evidence of Pulmonary Hypertension		
Attorney Docket Number	26047-0003011	Small Entity Status Claimed	☒
Application Type	Nonprovisional		
Subject Matter	Utility		
Total Number of Drawing Sheets (if any)		Suggested Figure for Publication (if any)	

Filing By Reference :

PTO/AIA/14 (12-13)
Approved for use through 01/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	26047-0003011
	Application Number	
Title of Invention	Methods of Treating Term and Near-Term Neonates Having Hypoxic Respiratory Failure Associated with Clinical or Echocardiographic Evidence of Pulmonary Hypertension	

Only complete this section when filing an application by reference under 35 U.S.C. 111(c) and 37 CFR 1.57(a). Do not complete this section if application papers including a specification and any drawings are being filed. Any domestic benefit or foreign priority information must be provided in the appropriate section(s) below (i.e., "Domestic Benefit/National Stage Information" and "Foreign Priority Information").

For the purposes of a filing date under 37 CFR 1.53(b), the description and any drawings of the present application are replaced by this reference to the previously filed application, subject to conditions and requirements of 37 CFR 1.57(a).

Application number of the previously filed application	Filing date (YYYY-MM-DD)	Intellectual Property Authority or Country

Publication Information:

☐ Request Early Publication (Fee required at time of Request 37 CFR 1.219)

☐ **Request Not to Publish.** I hereby request that the attached application not be published under 35 U.S.C. 122(b) and certify that the invention disclosed in the attached application **has not and will not** be the subject of an application filed in another country, or under a multilateral international agreement, that requires publication at eighteen months after filing.

Representative Information:

Representative information should be provided for all practitioners having a power of attorney in the application. Providing this information in the Application Data Sheet does not constitute a power of attorney in the application (see 37 CFR 1.32).
Either enter Customer Number or complete the Representative Name section below. If both sections are completed the customer Number will be used for the Representative Information during processing.

Please Select One:	◉ Customer Number	○ US Patent Practitioner	○ Limited Recognition (37 CFR 11.9)
Customer Number	94169		

Domestic Benefit/National Stage Information:

This section allows for the applicant to either claim benefit under 35 U.S.C. 119(e), 120, 121, or 365(c) or indicate National Stage entry from a PCT application. Providing this information in the application data sheet constitutes the specific reference required by 35 U.S.C. 119(e) or 120, and 37 CFR 1.78.
When referring to the current application, please leave the application number blank.

Prior Application Status	Pending		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
	Continuation of	14/451057	2014-08-04
Prior Application Status	Patented		Remove

Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
14/451057	Continuation of	13/683417	2012-11-21	8795741	2014-08-05
Prior Application Status	Abandoned				Remove

PTO/AIA/14 (12-13)
Approved for use through 01/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	26047-0003011
	Application Number	
Title of Invention	Methods of Treating Term and Near-Term Neonates Having Hypoxic Respiratory Failure Associated with Clinical or Echocardiographic Evidence of Pulmonary Hypertension	

Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
13/683417	Continuation of	12/820866	2010-06-22
Prior Application Status	Abandoned		Remove

Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
12/820866	Continuation of	12/494598	2009-06-30
Prior Application Status	Patented		Remove

Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
13/683417	Continuation of	13/651660	2012-10-15	8431163	2013-04-30
Prior Application Status	Patented				Remove

Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
13/651660	Continuation of	12/821041	2010-06-22	8293284	2012-10-23
Prior Application Status	Abandoned				Remove

Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
12/821041	Continuation of	12/494598	2009-06-30
Prior Application Status	Pending		Remove

Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
14/451057	Division of	13/683444	2012-11-21
Prior Application Status	Abandoned		Remove

Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
13/683444	Division of	12/820866	2010-06-22
Prior Application Status	Abandoned		Remove

Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
12/820866	Continuation of	12/494598	2009-06-30
Prior Application Status	Patented		Remove

Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
13/683444	Division of	13/651660	2012-10-15	8431163	2013-04-30
Prior Application Status	Patented				Remove

Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
13/651660	Continuation of	12/821041	2010-06-22	8293284	2012-10-23
Prior Application Status	Abandoned				Remove

Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
12/821041	Continuation of	12/494598	2009-06-30
Prior Application Status	Pending		Remove

PTO/AIA/14 (12-13)
Approved for use through 01/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	26047-0003011
	Application Number	
Title of Invention	Methods of Treating Term and Near-Term Neonates Having Hypoxic Respiratory Failure Associated with Clinical or Echocardiographic Evidence of Pulmonary Hypertension	

Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
	Division of	13/683444	2012-11-21
Prior Application Status	Abandoned		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
13/683444	Division of	12/820866	2010-06-22
Prior Application Status	Abandoned		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
12/820866	Continuation of	12/494598	2009-06-30
Prior Application Status	Patented		Remove

Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
13/683444	Division of	13/651660	2012-10-15	8431163	2013-04-30
Prior Application Status	Patented				Remove

Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
13/651660	Continuation of	12/821041	2010-06-22	8293284	2012-10-23
Prior Application Status	Abandoned				Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)		
12/821041	Continuation of	12/494598	2009-06-30		

Additional Domestic Benefit/National Stage Data may be generated within this form by selecting the **Add** button. Add

Foreign Priority Information:

This section allows for the applicant to claim priority to a foreign application. Providing this information in the application data sheet constitutes the claim for priority as required by 35 U.S.C. 119(b) and 37 CFR 1.55(d). When priority is claimed to a foreign application that is eligible for retrieval under the priority document exchange program (PDX) [i] the information will be used by the Office to automatically attempt retrieval pursuant to 37 CFR 1.55(h)(1) and (2). Under the PDX program, applicant bears the ultimate responsibility for ensuring that a copy of the foreign application is received by the Office from the participating foreign intellectual property office, or a certified copy of the foreign priority application is filed, within the time period specified in 37 CFR 1.55(g)(1).

Remove

Application Number	Country [i]	Filing Date (YYYY-MM-DD)	Access Code [i] (if applicable)

Additional Foreign Priority Data may be generated within this form by selecting the **Add** button. Add

PTO/AIA/14 (12-13)
Approved for use through 01/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	26047-0003011
	Application Number	
Title of Invention	Methods of Treating Term and Near-Term Neonates Having Hypoxic Respiratory Failure Associated with Clinical or Echocardiographic Evidence of Pulmonary Hypertension	

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications

☐ This application (1) claims priority to or the benefit of an application filed before March 16, 2013 and (2) also contains, or contained at any time, a claim to a claimed invention that has an effective filing date on or after March 16, 2013.
NOTE: By providing this statement under 37 CFR 1.55 or 1.78, this application, with a filing date on or after March 16, 2013, will be examined under the first inventor to file provisions of the AIA.

Authorization to Permit Access:

☐ Authorization to Permit Access to the Instant Application by the Participating Offices

If checked, the undersigned hereby grants the USPTO authority to provide the European Patent Office (EPO), the Japan Patent Office (JPO), the Korean Intellectual Property Office (KIPO), the World Intellectual Property Office (WIPO), and any other intellectual property offices in which a foreign application claiming priority to the instant patent application is filed access to the instant patent application. See 37 CFR 1.14(c) and (h). This box should not be checked if the applicant does not wish the EPO, JPO, KIPO, WIPO, or other intellectual property office in which a foreign application claiming priority to the instant patent application is filed to have access to the instant patent application.

In accordance with 37 CFR 1.14(h)(3), access will be provided to a copy of the instant patent application with respect to: 1) the instant patent application-as-filed; 2) any foreign application to which the instant patent application claims priority under 35 U.S.C. 119(a)-(d) if a copy of the foreign application that satisfies the certified copy requirement of 37 CFR 1.55 has been filed in the instant patent application; and 3) any U.S. application-as-filed from which benefit is sought in the instant patent application.

In accordance with 37 CFR 1.14(c), access may be provided to information concerning the date of filing this Authorization.

Applicant Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

PTO/AIA/14 (12-13)
Approved for use through 01/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	26047-0003011
	Application Number	
Title of Invention	Methods of Treating Term and Near-Term Neonates Having Hypoxic Respiratory Failure Associated with Clinical or Echocardiographic Evidence of Pulmonary Hypertension	

Applicant 1 Remove

If the applicant is the inventor (or the remaining joint inventor or inventors under 37 CFR 1.45), this section should not be completed. The information to be provided in this section is the name and address of the legal representative who is the applicant under 37 CFR 1.43; or the name and address of the assignee, person to whom the inventor is under an obligation to assign the invention, or person who otherwise shows sufficient proprietary interest in the matter who is the applicant under 37 CFR 1.46. If the applicant is an applicant under 37 CFR 1.46 (assignee, person to whom the inventor is obligated to assign, or person who otherwise shows sufficient proprietary interest) together with one or more joint inventors, then the joint inventor or inventors who are also the applicant should be identified in this section.

Clear

◉ Assignee	○ Legal Representative under 35 U.S.C. 117	○ Joint Inventor
○ Person to whom the inventor is obligated to assign.	○ Person who shows sufficient proprietary interest	

If applicant is the legal representative, indicate the authority to file the patent application, the inventor is:

Name of the Deceased or Legally Incapacitated Inventor :

If the Applicant is an Organization check here. ☒

Organization Name	INO Therapeutics LLC

Mailing Address Information:

Address 1	Perryville III, Corporate Park		
Address 2	53 Frontage Road		
City	Hampton	**State/Province**	NJ
Country [i]	US	Postal Code	08827
Phone Number		Fax Number	
Email Address			

Additional Applicant Data may be generated within this form by selecting the Add button. Add

Assignee Information including Non-Applicant Assignee Information:

Providing assignment information in this section does not subsitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

Assignee 1

Complete this section if assignee information, including non-applicant assignee information, is desired to be included on the patent application publication . An assignee-applicant identified in the "Applicant Information" section will appear on the patent application publication as an applicant. For an assignee-applicant, complete this section only if identification as an assignee is also desired on the patent application publication.

Remove

If the Assignee or Non-Applicant Assignee is an Organization check here. ☒

PTO/AIA/14 (12-13)
Approved for use through 01/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	26047-0003011
	Application Number	
Title of Invention	Methods of Treating Term and Near-Term Neonates Having Hypoxic Respiratory Failure Associated with Clinical or Echocardiographic Evidence of Pulmonary Hypertension	

Organization Name	INO Therapeutics LLC

Mailing Address Information For Assignee including Non-Applicant Assignee:

Address 1	Perryville III, Corporate Park		
Address 2	53 Frontage Road, Third Floor		
City	Hampton	**State/Province**	NJ
Country i	US	Postal Code	08827
Phone Number		Fax Number	
Email Address			

Additional Assignee or Non-Applicant Assignee Data may be generated within this form by selecting the Add button. Add

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First Name	Janis	Last Name	Fraser	Registration Number	34819

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METHODS OF TREATING TERM AND NEAR-TERM NEONATES HAVING HYPOXIC RESPIRATORY FAILURE ASSOCIATED WITH CLINICAL OR ECHOCARDIOGRAPHIC EVIDENCE OF PULMONARY HYPERTENSION

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] Not applicable.

STATEMENT CONCERNING GOVERNMENT INTEREST

[0002] Not applicable.

BACKGROUND OF THE INVENTION

[0003] INOmax®, (nitric oxide) for inhalation is an approved drug product for the treatment of term and near-term (>34 weeks gestation) neonates having hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension.

[0004] The use of inhaled NO (iNO) has been studied and reported in the literature. (Kieler-Jensen M et al., 1994, Inhaled Nitric Oxide in the Evaluation of Heart Transplant Candidates with Elevated Pulmonary Vascular Resistance, *J Heart Lung Transplantation* 13:366-375; Pearl RG et al., 1983, Acute Hemodynamic Effects of Nitroglycerin in Pulmonary Hypertension, *American College of Physicians* 99:9-13; Ajami GH et al., 2007, Comparison of the Effectiveness of Oral Sildenafil Versus Oxygen Administration as a Test for Feasibility of Operation for Patients with Secondary Pulmonary Arterial Hypertension, *Pediatr Cardiol*; Schulze-Neick I et al., 2003, Intravenous Sildenafil Is a Potent Pulmonary Vasodilator in Children With Congenital Heart Disease, *Circulation* 108(Suppl II):II-167-II-173; Lepore JJ et al., 2002, Effect of Sildenafil on the Acute Pulmonary Vasodilator Response to Inhaled Nitric Oxide in Adults with Primary Pulmonary Hypertension, *The American Journal of Cardiology* 90:677-680; and Ziegler JW et al., 1998, Effects of Dipyridamole and Inhaled Nitric Oxide in Pediatric Patients with Pulmonary Hypertension, *American Journal of Respiratory and Critical Care Medicine* 158:1388-95).

SUMMARY OF THE INVENTION

[0005] One aspect of the invention relates to a pre-screening methodology or protocol having exclusionary criteria to be evaluated by a medical provider prior to treatment of a patient with iNO. One objective of the invention is to evaluate and possibly exclude from treatment patients eligible for treatment with iNO, who have pre-existing left ventricular dysfunction (LVD). Patients who have pre-existing LVD may experience, and are at risk of, an increased rate of adverse events or serious adverse events (e.g., pulmonary edema) when treated with iNO. Such patients may be characterized as having a pulmonary capillary wedge pressure (PCWP) greater than 20 mm Hg, and should be evaluated on a case-by-case basis with respect to the benefit versus risk of using iNO as a treatment option.

[0006] Accordingly, one aspect of the invention includes a method of reducing the risk or preventing the occurrence, in a human patient, of an adverse event (AE) or a serious adverse event (SAE) associated with a medical treatment comprising inhalation of nitric oxide, said method comprising the steps or acts of (a) providing pharmaceutically acceptable nitric oxide gas to a medical provider; and, (b) informing the medical provider that excluding human patients who have pre-existing left ventricular dysfunction from said treatment reduces the risk or prevents the occurrence of the adverse event or the serious adverse event associated with said medical treatment.

[0007] Further provided herein is a method of reducing the risk or preventing the occurrence, in a human patient, of an adverse event or a serious adverse event associated with a medical treatment comprising inhalation of nitric oxide, said method comprising the steps or acts of (a.) providing pharmaceutically acceptable nitric oxide gas to a medical provider; and, (b.) informing the medical provider that human patients having pre-existing left ventricular dysfunction experience an increased risk of serious adverse events associated with said medical treatment.

[0008] Another aspect of the invention is a method of reducing one or more of an AE or a SAE in an intended patient population in need of being treated with iNO comprising the steps or acts of (a.) identifying a patient eligible for iNO treatment; (b) evaluating and screening the patient to identify if the patient has pre-existing LVD, and (c) excluding from iNO treatment a patient identified as having pre-existing LVD.

[0009] Another aspect of the invention is a method of reducing the risk or preventing the occurrence, in a patient, of one or more of an AE or a SAE associated with a medical treatment comprising iNO, the method comprising the steps or acts of (a.) identifying a patient in need of receiving iNO treatment; (b.) evaluating and screening the patient to identify if the patient has pre-existing LVD; and (c.)administering iNO if the patient does not have pre-existing LVD, thereby reducing the risk or preventing the occurrence of the AE or the SAE associated with the iNO treatment. Alternatively, step (c) may comprise further evaluating the risk versus benefit of utilizing iNO in a patient where the patients has clinically significant LVD before administering iNO to the patient.

[0010] In an exemplary embodiment of the method, the method further comprises informing the medical provider that there is a risk associated with using inhaled nitric oxides in human patients who have preexisting or clinically significant left ventricular dysfunction and that such risk should be evaluated on a case by case basis.

[0011] In another exemplary embodiment of the method, the method further comprises informing the medical provider that there is a risk associated with using inhaled nitric oxide in human patients who have left ventricular dysfunction.

[0012] In an exemplary embodiment of the methods described herein, a patient having pre-existing LVD is characterized as having PCWP greater than 20 mm Hg.

[0013] In an exemplary embodiment of the method, the patients having pre-existing LVD demonstrate a PCWP $\geq$ 20 mm Hg.

[0014] In another exemplary embodiment of the method, the iNO treatment further comprises inhalation of oxygen (O_2) or concurrent ventilation.

[0015] In another exemplary embodiment of the method, the patients having pre-existing LVD have one or more of diastolic dysfunction, hypertensive cardiomyopathy, systolic dysfunction, ischemic cardiomyopathy, viral cardiomyopathy, idiopathic cardiomyopathy, autoimmune disease related cardiomyopathy, drug-related cardiomyopathy, toxin-related cardiomyopathy, structural heart disease, valvular heart disease, congenital heart disease, or, associations thereof.

[0016] In another exemplary embodiment of the method, the patient population comprises children.

[0017] In another exemplary embodiment of the method, the patient population comprises adults.

[0018] In another exemplary embodiment of the method, the patients who have pre-existing LVD are at risk of experiencing and increased rate of one or more AEs or SAEs selected from pulmonary edema, hypotension, cardiac arrest, electrocardiogram changes, hypoxemia, hypoxia, bradycardia or associations thereof.

[0019] In another exemplary embodiment of the method, the intended patient population in need of being treated with inhalation of nitric oxide has one or more of idiopathic pulmonary arterial hypertension characterized by a mean pulmonary artery pressure (PAPm) > 25 mm Hg at rest, PCWP $\leq$ 15 mm Hg, and, a pulmonary vascular resistance index (PVRI) > 3 u·m^2; congenital heart disease with pulmonary hypertension repaired and unrepaired characterized by PAPm > 25 mm Hg at rest and PVRI > 3 u·m^2; cardiomyopathy characterized by PAPm > 25 mm Hg at rest and PVRI > 3 u·m^2; or, the patient is scheduled to undergo right heart catheterization to assess pulmonary vasoreactivity by acute pulmonary vasodilatation testing.

[0020] In another exemplary embodiment of any of the above methods, the method further comprises reducing left ventricular afterload to minimize or reduce the risk of the occurrence of an adverse event or serious adverse event being pulmonary edema in the patient. The left ventricular afterload may be minimized or reduced by administering a pharmaceutical dosage form comprising nitroglycerin or calcium channel blocker to the patient. The left ventricular afterload may also be minimized or reduced using an intra-aortic balloon pump.

DETAILED DESCRIPTION OF THE EXEMPLARY EMBODIMENTS

[0021] INOmax® (nitric oxide) for inhalation was approved for sale in the United States by the U.S. Food and Drug Administration ("FDA") in 1999. Nitric oxide, the active substance in INOmax®, is a selective pulmonary vasodilator that increases the partial pressure of arterial oxygen (PaO_2) by dilating pulmonary vessels in better ventilated areas of the lung, redistributing pulmonary blood flow away from the lung regions with low ventilation/perfusion (V/Q) ratios toward regions with normal ratios. INOmax® significantly improves oxygenation, reduces the need for extracorporeal oxygenation and is indicated to be used in conjunction with ventilatory support and other appropriate agents. The current FDA-approved prescribing information for INOmax® is incorporated herein by reference in its entirety.

[0022] INOmax® is a gaseous blend of NO and nitrogen (0.08% and 99.92% respectively for 800 ppm; and 0.01% and 99.99% respectively for 100 ppm) and is supplied in aluminium cylinders as a compressed gas under high pressure. In general, INOmax® is administered to a patient in conjunction with ventilatory support and O_2. Delivery devices suitable for the safe and effective delivery of gaseous NO for inhalation include the INOvent®, INOmax DS®, INOpulse®, INOblender®, or other suitable drug delivery and regulation devices or components incorporated therein, or other related processes, which are described in various patent documents including USPNs 5,558,083; 5,732,693; 5,752,504; 5,732,694; 6,089,229; 6,109,260; 6,125,846; 6,164,276; 6,581,592; 5,918,596; 5,839,433; 7,114,510; 5,417;950; 5,670,125; 5,670,127; 5,692,495; 5,514,204; 7,523,752; 5,699,790; 5,885,621; US Patent Application Serial Nos. 11/355,670 (US 2007/0190184); 10/520,270 (US 2006/0093681); 11/401,722 (US 2007/0202083); 10/053,535 (US 2002/0155166); 10/367,277 (US 2003/0219496); 10/439,632 (US 2004/0052866); 10/371,666 (US 2003/0219497); 10/413,817 (US 2004/0005367); 12/050,826 (US 2008/0167609); and PCT/US2009/045266, all of which are incorporated herein by reference in their entirety.

[0023] Such devices deliver INOmax® into the inspiratory limb of the patient breathing circuit in a way that provides a constant concentration of NO to the patient throughout the inspired breath. Importantly, suitable delivery devices provide continuous integrated monitoring of inspired O_2, NO_2 and NO, a comprehensive alarm system, a suitable power source for uninterrupted NO delivery and a backup NO delivery capability.

[0024] As used herein, the term "children" (and variations thereof) includes those being around 4 weeks to 18 years of age.

[0025] As used herein, the term "adult" (and variations thereof) includes those being over 18 years of age.

[0026] As used herein, the terms "adverse event" or "AE" (and variations thereof) mean any untoward occurrence in a subject, or clinical investigation subject administered a pharmaceutical product (such as nitric oxide) and which does not necessarily have a causal relationship with such treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporarily associated with the use of a medicinal/investigational product, whether or not related to the

investigational product. A relationship to the investigational product is not necessarily proven or implied. However, abnormal values are not reported as adverse events unless considered clinically significant by the investigator.

[0027] As used herein, the terms "adverse drug reaction" or "ADR" (and variations thereof) mean any noxious and unintended response to a medicinal product related to any dose.

[0028] As used herein, the terms "serious adverse event" or "SAE" (or "serious adverse drug reaction" or "serious ADR") (and variations thereof) mean a significant hazard or side effect, regardless of the investigator's opinion on the relationship to the investigational product. A serious adverse event or reaction is any untoward medical occurrence that at any dose: results in death; is life-threatening (which refers to an event/reaction where the patient was at risk of death at the time of the event/reaction, however this does not refer to an event/reaction that hypothetically may have caused death if it were more severe); requires inpatient hospitalization or results in prolongation of existing hospitalization; results in persistent or significant disability/incapacity; is a congenital anomaly/birth defect; or, is a medically important event or reaction. Medical and scientific judgment is exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed above--these are also considered serious. Examples of such medical events include cancer, allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in hospitalizations, or the development of drug dependency or drug abuse. Serious clinical laboratory abnormalities directly associated with relevant clinical signs or symptoms are also reported.

[0029] Left Ventricular Dysfunction. Patients having pre-existing LVD may be described in general as those with elevated pulmonary capillary wedge pressure, including those with diastolic dysfunction (including hypertensive cardiomyopathy), those with systolic dysfunction, including those with cardiomyopathies (including ischemic or viral cardiomyopathy, or idiopathic cardiomyopathy, or autoimmune disease related cardiomyopathy, and side effects due to drug related or toxic-related cardiomyopathy), or structural heart disease, valvular heart disease, congenital heart disease, idiopathic pulmonary arterial hypertension,

pulmonary hypertension and cardiomyopathy, or associations thereof. Identifying patients with pre-existing LVD is known to those skilled in the medicinal arts, and such techniques for example may include assessment of clinical signs and symptoms of heart failure, or echocardiography diagnostic screening.

[0030] Pulmonary Capillary Wedge Pressure. Pulmonary capillary wedge pressure, or "PCWP", provides an estimate of left atrial pressure. Identifying patients with pre-existing PCWP is known to those skilled in the medicinal arts, and such techniques for example may include measure by inserting balloon-tipped, multi-lumen catheter (also known as a Swan-Ganz catheter). Measure of PCWP may be used as a means to diagnose the severity of LVD (sometimes also referred to as left ventricular failure). PCWP is also a desired measure when evaluating pulmonary hypertension. Pulmonary hypertension is often caused by an increase in pulmonary vascular resistance (PVR), but may also arise from increases in pulmonary venous pressure and pulmonary blood volume secondary to left ventricular failure or mitral or aortic valve disease.

[0031] In cardiac physiology, afterload is used to mean the tension produced by a chamber of the heart in order to contract. If the chamber is not mentioned, it is usually assumed to be the left ventricle. However, the strict definition of the term relates to the properties of a single cardiac myocyte. It is therefore only of direct relevance in the laboratory; in the clinic, the term end-systolic pressure is usually more appropriate, although not equivalent.

[0032] The terms "left ventricular afterload" (and variations thereof) refer to the pressure that the chamber of the heart has to generate in order to eject blood out of the chamber. Thus, it is a consequence of the aortic pressure since the pressure in the ventricle must be greater than the systemic pressure in order to open the aortic valve. Everything else held equal, as afterload increases, cardiac output decreases. Disease processes that increase the left ventricular afterload include increased blood pressure and aortic valve disease. Hypertension (Increased blood pressure) increases the left ventricular afterload because the left ventricle has to work harder to eject blood into the aorta. This is because the aortic valve won't open until the pressure generated in the left ventricle is higher than the elevated blood pressure. Aortic stenosis increases the afterload because the left ventricle has to overcome the pressure gradient caused by the stenotic aortic valve in addition to the blood pressure in order to eject blood into the

aorta. For instance, if the blood pressure is 120/80, and the aortic valve stenosis creates a trans-valvular gradient of 30 mmHg, the left ventricle has to generate a pressure of 110 mmHg in order to open the aortic valve and eject blood into the aorta. Aortic insufficiency increases afterload because a percentage of the blood that is ejected forward regurgitates back through the diseased aortic valve. This leads to elevated systolic blood pressure. The diastolic blood pressure would fall, due to regurgitation. This would result in an increase pulse pressure. Mitral regurgitation decreases the afterload. During ventricular systole, the blood can regurgitate through the diseased mitral valve as well as be ejected through the aortic valve. This means that the left ventricle has to work less to eject blood, causing a decreased afterload. Afterload is largely dependent upon aortic pressure.

[0033] An intra-aortic balloon pump (IABP) is a mechanical device that is used to decrease myocardial oxygen demand while at the same time increasing cardiac output. By increasing cardiac output it also increases coronary blood flow and therefore myocardial oxygen delivery. It consists of a cylindrical balloon that sits in the aorta and counterpulsates. That is, it actively deflates in systole increasing forward blood flow by reducing afterload thus, and actively inflates in diastole increasing blood flow to the coronary arteries. These actions have the combined result of decreasing myocardial oxygen demand and increasing myocardial oxygen supply. The balloon is inflated during diastole by a computer controlled mechanism, usually linked to either an ECG or a pressure transducer at the distal tip of the catheter; some IABPs, such as the Datascope System 98XT, allow for asynchronous counterpulsation at a set rate, though this setting is rarely used. The computer controls the flow of helium from a cylinder into and out of the balloon. Helium is used because its low viscosity allows it to travel quickly through the long connecting tubes, and has a lower risk of causing a harmful embolism should the balloon rupture while in use. Intraaortic balloon counterpulsation is used in situations when the heart's own cardiac output is insufficient to meet the oxygenation demands of the body. These situations could include cardiogenic shock, severe septic shock, post cardiac surgery and numerous other situations.

[0034] Patients eligible for treatment with iNO. In general, patients approved for treatment of iNO are term and near-term (>34 weeks gestation) neonates having hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension, a condition also known as persistent pulmonary hypertension in the newborn

(PPHN). Due to the selective, non-systemic nature of iNO to reduce pulmonary hypertension, physicians skilled in the art further employ INOmax® to treat or prevent pulmonary hypertension and improve blood O_2 levels in a variety of other clinical settings, including in both pediatric and adult patients suffering from acute respiratory distress syndrome (ARDS), pediatric and adult patients undergoing cardiac or transplant surgeries, pediatric and adult patients for testing to diagnose reversible pulmonary hypertension, and in pediatric patients with congenital diaphragmatic hernia. In most, if not all, of these applications, INOmax® acts by preventing or treating reversible pulmonary vasoconstriction, reducing pulmonary arterial pressure and improving pulmonary gas exchange.

[0035] A small proportion of INOmax® sales stem from its use by clinicians in a premature infant population. In these patients, INOmax® is generally utilized by physicians as a rescue therapy primarily to vasodilate the lungs and improve pulmonary gas exchange. Some physicians speculate that INOmax® therapy may promote lung development and/or reduce or prevent the future development of lung disease in a subset of these patients. Although the precise mechanism(s) responsible for the benefits of INOmax® therapy in these patients is not completely understood, it appears that the benefits achieved in at least a majority of these patients are due to the ability of INOmax® to treat or prevent reversible pulmonary vasoconstriction.

[0036] In clinical practice, the use of INOmax® has reduced or eliminated the use of high risk systemic vasodilators for the treatment of PPHN. INOmax®, in contrast to systemic vasodilators, specifically dilates the pulmonary vasculature without dilating systemic blood vessels. Further, iNO preferentially vasodilates vessels of aveoli that are aerated, thus improving V/Q matching. In contrast, systemic vasodilators may increase blood flow to atelectatic (deflated or collapsed) alveoli, thereby increasing V/Q mismatch and worsening arterial oxygenation. (*See* Rubin LJ, Kerr KM, Pulmonary Hypertension, in *Critical Care Medicine: Principles of Diagnosis and Management in the Adult, 2d Ed.*, Parillo JE, Dellinger RP (eds.), Mosby, Inc. 2001, pp. 900-09 at 906; Kinsella JP, Abman SH, The Role of Inhaled Nitric Oxide in Persistent Pulmonary Hypertension of the Newborn, in *Acute Respiratory Care of the Neonate: A Self-Study Course, 2d Ed.*, Askin DF (ed.), NICU Ink Book Publishers, 1997, pp. 369-378 at 372-73).

[0037] INOmax® also possesses highly desirable pharmacokinetic properties as a lung-specific vasodilator when compared to other ostensibly "pulmonary-specific vasodilators." For example, the short half-life of INOmax® allows INOmax® to exhibit rapid "on" and "off" responses relative to INOmax® dosing, in contrast to non-gaseous alternatives. In this way, INOmax® can provide physicians with a useful therapeutic tool to easily control the magnitude and duration of the pulmonary vasodilatation desired. Also, the nearly instantaneous inactivation of INOmax® in the blood significantly reduces or prevents vasodilatation of non-pulmonary vessels.

[0038] The pivotal trials leading to the approval of INOmax® were the CINRGI and NINOS study.

[0039] CINRGI study. (See Davidson et al., March 1998, 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, No. 3, p. 325).

[0040] This study was a double-blind, randomized, placebo-controlled, multicenter trial of 186 term and near-term neonates with pulmonary hypertension and hypoxic respiratory failure. The primary objective of the study was to determine whether INOmax® would reduce the receipt of extracorporeal membrane oxygenation (ECMO) in these patients. Hypoxic respiratory failure was caused by meconium aspiration syndrome (MAS) (35%), idiopathic persistent pulmonary hypertension of the newborn (PPHN) (30%), pneumonia/sepsis (24%), or respiratory distress syndrome (RDS) (8%). Patients with a mean PaO_2 of 54 mm Hg and a mean oxygenation index (OI) of 44 cm H_2O/mm Hg were randomly assigned to receive either 20 ppm INOmax® (n=97) or nitrogen gas (placebo; n=89) in addition to their ventilatory support. Patients that exhibited a $PaO_2 > 60$ mm Hg and a $pH < 7.55$ were weaned to 5 ppm INOmax® or placebo. The primary results from the CINRGI study are presented in Table 4. ECMO was the primary endpoint of the study.

Table 1: Summary of Clinical Results from CINRGI Study

	Placebo	INOmax®	P value
Death or ECMO	51/89 (57%)	30/97 (31%)	<0.001
Death	5/89 (6%)	3/97 (3%)	0.48

[0041] Significantly fewer neonates in the ECMO group required ECMO, and INOmax® significantly improved oxygenation, as measured by PaO_2, OI, and alveolar-arterial gradient.

[0042] NINOS study. (See Inhaled Nitric Oxide in Full-Term and Nearly Full-Term Infants with Hypoxic Respiratory Failure; NEJM, Vol. 336, No. 9, 597).

[0043] The Neonatal Inhaled Nitric Oxide Study (NINOS) group conducted a double-blind, randomized, placebo-controlled, multicenter trial in 235 neonates with hypoxic respiratory failure. The objective of the study was to determine whether iNO would reduce the occurrence of death and/or initiation of ECMO in a prospectively defined cohort of term or near-term neonates with hypoxic respiratory failure unresponsive to conventional therapy. Hypoxic respiratory failure was caused by meconium aspiration syndrome (MAS; 49%), pneumonia/sepsis (21%), idiopathic primary pulmonary hypertension of the newborn (PPHN; 17%), or respiratory distress syndrome (RDS; 11%). Infants ≤ 14 days of age (mean, 1.7 days) with a mean PaO_2 of 46 mm Hg and a mean oxygenation index (OI) of 43 cm H_2O/mmHg were initially randomized to receive 100% O_2 with (n=114) or without (n=121) 20 ppm NO for up to 14 days. Response to study drug was defined as a change from baseline in PaO_2 30 minutes after starting treatment (full response = > 20 mmHg, partial = 10–20 mm Hg, no response = < 10 mm Hg). Neonates with a less than full response were evaluated for a response to 80 ppm NO or control gas. The primary results from the NINOS study are presented in Table 2.

Table 2: Summary of Clinical Results from NINOS Study

	Control (n=121)	NO (n=114)	P value
Death or ECMO*, †	77 (64%)	52 (46%)	0.006
Death	20 (17%)	16 (14%)	0.60
ECMO	66 (55%)	44 (39%)	0.014

* Extracorporeal membrane oxygenation
† Death or need for ECMO was the study's primary end point

[0044] Adverse Events from CINRGI & NINOS. Controlled studies have included 325 patients on INOmax® doses of 5 to 80 ppm and 251 patients on placebo. Total mortality in the pooled trials was 11% on placebo and 9% on INOmax®, a result adequate to exclude INOmax® mortality being more than 40% worse than placebo.

[0045] In both the NINOS and CINRGI studies, the duration of hospitalization was similar in INOmax® and placebo-treated groups.

[0046] From all controlled studies, at least 6 months of follow-up is available for 278 patients who received INOmax® and 212 patients who received placebo. Among these patients, there was no evidence of an AE of treatment on the need for re-hospitalization, special medical services, pulmonary disease, or neurological squeal.

[0047] In the NINOS study, treatment groups were similar with respect to the incidence and severity of intracranial hemorrhage, Grade IV hemorrhage, per ventricular leukomalacia, cerebral infarction, seizures requiring anticonvulsant therapy, pulmonary hemorrhage, or gastrointestinal hemorrhage.

[0048] The table below shows adverse reactions that occurred in at least 5% of patients receiving INOmax® in the CINRGI study. None of the differences in these adverse reactions were statistically significant when iNO patients were compared to patients receiving placebo.

Table 3: ADVERSE REACTIONS ON THE CINRGI TRIAL

Adverse Reaction	Placebo (n=89)	Inhaled NO (n=97)
Atelectasis	5 (4.8%)	7 (6.5%)
Bilirubinemia	6 (5.8%)	7 (6.5%)
Hypokalemia	5 (4.8%)	9 (8.3%)
Hypotension	3 (2.9%)	6 (5.6%)
Thrombocytopenia	20 (19.2%)	16 (14.8%)

[0049] Post-Marketing Experience. The following AEs have been reported as part of the post-marketing surveillance. These events have not been reported above. Given the nature of spontaneously reported post-marketing surveillance data, it is impossible to determine the actual incidence of the events or definitively establish their causal relationship to the drug. The listing is alphabetical: dose errors associated with the delivery system; headaches associated with environmental exposure of INOmax® in hospital staff; hypotension associated with acute withdrawal of the drug; hypoxemia associated with acute withdrawal of the drug; pulmonary edema in patients with CREST syndrome.

[0050] An analysis of AEs and SAEs from both the CINRGI and NINOS studies, in addition to post-marketing surveillance, did not suggest that patients who have pre-existing LVD could experience an increased risk of AEs or SAEs. Nor was it predictable to physicians skilled in the art that patients having pre-existing LVD (possibly identified as those patients having a PCWP greater than 20 mmHg) should be evaluated in view of the benefit versus risk of using iNO in patients with clinically significant LVD, and that these patients should be evaluated on a case by case basis.

EXAMPLE 1: INOT22 STUDY

[0051] The INOT22, 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 vasodilatory testing" was conducted both to access the safety and effectiveness

of INOmax® as a diagnostic agent in patients undergoing assessment of pulmonary hypertension (primary endpoint), and to confirm the hypothesis that iNO is selective for the pulmonary vasculature (secondary endpoint).

[0052] During, and upon final analysis of the INOT22 study results, applicants discovered that rapidly decreasing the pulmonary vascular resistance, via the administration of iNO to a patient in need of such treatment, may be detrimental to patients with concomitant, pre-existing LVD. Therefore, a precaution for patients with LVD was proposed to be included in amended prescribing information for INOmax®. Physicians were further informed to consider reducing left ventricular afterload to minimize the occurrence of pulmonary edema in patients with pre-existing LVD.

[0053] In particular, the INOT22 protocol studied consecutive children undergoing cardiac catheterization that were prospectively enrolled at 16 centers in the US and Europe. Inclusion criteria: 4 weeks to 18 years of age, pulmonary hypertension diagnosis, i.e. either idiopathic pulmonary hypertension (IPAH) or related to congenital heart disease (CHD) (repaired or unrepaired) or cardiomyopathy, with pulmonary vascular resistance index (PVRI) > 3 u-m^2. Later amendments, as discussed herein, added an additional inclusionary criteria of a PCWP less than 20 gmm Hg. Patients were studied under general anaesthesia, or with conscious sedation, according to the practice of the investigator. Exclusion criteria: focal infiltrates on chest X-ray, history of intrinsic lung disease, and/or currently taking PDE-5 inhibitors, prostacyclin analogues or sodium nitroprusside. The study involved supplemental O_2 and NO for inhalation plus O_2 in the evaluation of the reactivity of the pulmonary vasculature during acute pulmonary vasodilator testing. Consecutive children undergoing cardiac catheterization were prospectively enrolled at 16 centers in the US and Europe. As hypotension is expected in these neonatal populations, the comparison between iNO and placebo groups is difficult to assess. A specific secondary endpoint was evaluated in study INOT22 to provide a more definitive evaluation.

[0054] The primary objective was to compare the response frequency with iNO and O_2 vs. O_2 alone; in addition, all subjects were studied with iNO alone. Patients were studied during five periods: Baseline 1, Treatment Period 1, Treatment Period 2, Baseline 2 and Treatment Period 3. All patients received all three treatments; treatment sequence was randomized by

center in blocks of 4; in Period 1, patients received either NO alone or O_2 alone, and the alternate treatment in Period 3. All patients received the iNO and O_2 combination treatment in Period 2. Once the sequence was assigned, treatment was unblinded. Each treatment was given for 10 minutes prior to obtaining hemodynamic measurements, and the Baseline Period 2 was at least 10 minutes.

[0055] Results for the intent-to-treat (ITT) population, defined as all patients who were randomized to receive drug, indicated that treatment with NO plus O_2 and O_2 alone significantly increased systemic vascular resistance index (SVRI) (Table 4). The change from baseline for NO plus O_2 was 1.4 Woods Units per meter^2 (WU·m^2) ($p = 0.007$) and that for O_2 was 1.3 WU·m^2 ($p = 0.004$). While the change from baseline in SVRI with NO alone was -0.2 WU·m^2 ($p = 0.899$) which demonstrates a lack of systemic effect.

Table 4: SVRI Change From Baseline by Treatment (Intent-to-Treat)

	Treatment		
SVRI ($WU \cdot m^2$)	**NO Plus O_2 (n=109)**	**O_2 (n=106)**	**NO (n=106)**
Baseline (room air)			
Mean	17.2	17.6	18.0
Standard Deviation (SD)	8.86	9.22	8.44
Median	15.9	16.1	16.2
Minimum, maximum	-7.6, 55.6	-7.6, 55.6	1.9, 44.8
Post-treatment			
Mean	18.7	18.9	17.8
SD	9.04	8.78	9.40
Median	17.1	17.1	15.4
Minimum, maximum	3.0, 47.4	3.9, 43.6	3.3, 50.7
Change From Baseline			
Mean	1.4	1.3	-0.2
SD	5.94	5.16	4.65
Median	1.2	1.0	0.2
Minimum, maximum	-20.5, 19.1	-18.1, 17.7	-12.5, 12.7
p-value[a]	0.007	0.004	0.899
Pairwise comparisons NO plus O_2 versus O_2, p=0.952 NO plus O_2 versus NO, p=0.014 O_2 versus NO, p=0.017			

[a] p-value from a Wilcoxon Signed Rank Test. Only patients with data to determine response at both treatments are included in this analysis.

Source: INOT22 CSR Table 6.4.1 and Appendix 16.2.6 (ATTACHMENT 1)

[0056] The ideal pulmonary vasodilator should reduce PVRI and/or PAPm while having no appreciable effect on systemic blood pressure or SVRI. In this case, the ratio of PVRI to SVRI would decrease, given some measure of the selectivity of the agent for the pulmonary vascular bed. The change in the ratio of PVRI to SVRI by treatment is shown in Table 5.

Table 5: Change in Ratio of PVRI to SVRI by Treatment (Intent-to-Treat)

	Treatment		
Ratio PVRI/SVRI	**NO Plus O_2 (n=108)**	**O_2 (n=105)**	**NO (n=106)**
Baseline			
Mean	0.6	0.5	0.6
SD	0.60	0.45	0.56
Median	0.5	0.5	0.4
Minimum, Maximum	-1.6, 4.7	-1.6, 1.8	0.0, 4.7
Post Treatment			
Mean	0.4	0.4	0.5
SD	0.31	0.31	0.46
Median	0.3	0.4	0.3
Minimum, Maximum	0.0, 1.3	0.0, 1.4	-1.2, 2.2
Change from Baseline			
Mean	-0.2	-0.1	-0.1
SD	0.52	0.31	0.54
Median	-0.1	-0.1	0.0
Minimum, Maximum	-4.4, 2.0	-1.6, 2.0	-4.4, 1.6
P Value[1]	< 0.001	< 0.001	0.002

[1] Wilcoxon Signed Rank Test
Source: INOT22 CSR Table 6.5.1 (ATTACHMENT 2)

[0057] All three treatments have a preferential effect on the pulmonary vascular bed, suggesting that all three are selective pulmonary vasodilators. The greatest reduction in the ratio was during treatment with NO plus O_2, possibly due to the decrease in SVRI effects seen with O_2 and NO plus O_2. These results are displayed as percent change in the ratio (See Table 6).

Table 6: Percent Change in Ratio of PVRI to SVRI by Treatment (Intent-to-Treat)

	Treatment		
Ratio PVRI/SVRI	**NO Plus O_2 (n=108)**	**O_2 (n=105)**	**NO (n=106)**
Baseline			
Mean	0.6	0.5	0.6
SD	0.60	0.45	0.56
Median	0.5	0.5	0.4
Minimum, Maximum	-1.6, 4.7	-1.6, 1.8	0.0, 4.7
Post Treatment			
Mean	0.4	0.4	0.5
SD	0.31	0.31	0.46
Median	0.3	0.4	0.3
Minimum, Maximum	0.0, 1.3	0.0, 1.4	-1.2, 2.2
Percent Change from Baseline			
Mean	-33.5	-19.3	-6.2
SD	36.11	34.59	64.04
Median	-34.0	-21.3	-13.8
Minimum, Maximum	-122.2, 140.1	-122.7, 93.3	-256.1, 294.1
P Value[1]	< 0.001	< 0.001	0.006

[1] Wilcoxon Signed Rank Test
Source: INOT22 CSR Table 6.5.2 (ATTACHMENT 3)

[0058] NO plus O_2 appeared to provide the greatest reduction in the ratio, suggesting that NO plus O_2 was more selective for the pulmonary vasculature than either agent alone.

[0059] Overview of Cardiovascular Safety. In the INOT22 diagnostic study, all treatments (NO plus O_2, O_2, and NO) were well-tolerated. Seven patients of 134 treated experienced an AE during the study. These included cardiac arrest, bradycardia, low cardiac output (CO) syndrome, elevated ST segment (the portion of an electrocardiogram between the end of the QRS complex and the beginning of the T wave) on the electrocardiography (ECG)

decreased O_2 saturation, hypotension, mouth hemorrhage and pulmonary hypertension (PH). The numbers of patients and events were too small to determine whether risk for AEs differed by treatment, diagnosis, age, gender or race. Eight patients are shown in Table 5 due to the time period in which events are reported. AEs were reported for 12 hours or until hospital discharge (which limits the period in which such events can be reported). There is technically no time limit in which SAEs are to be reported. So, there were 7 AEs during the study and at least one SAE after the study.

[0060] A total of 4 patients had AEs assessed as being related to study drug. These events included bradycardia, low CO syndrome, ST segment elevation on the ECG, low O_2 saturation, PH and hypotension. All but 2 AEs were mild or moderate in intensity and were resolved. Study treatments had slight and non-clinically significant effects on vital signs including heart rate, systolic arterial pressure and diastolic arterial pressure. When an investigator records an AE, they are required to say if (in their opinion) the event is related to the treatment or not. In this case, 4 of 7 were considered by the investigator to be related to treatment.

[0061] The upper limit of normal PCWP in children is 10-12 mm Hg and 15 mm Hg in adults. In INOT22, a baseline PCWP value was not included as exclusion criteria. However, after the surprising and unexpected identification of SAEs in the early tested patients, it was determined that patients with pre-existing LVD had an increased risk of experiencing an AE or SAE upon administration (e.g., worsening of left ventricular function due to the increased flow of blood through the lungs). Accordingly, the protocol for INOT22 was thereafter amended to exclude patients with a baseline PCWP greater than 20 mm Hg after one patient experienced acute circulatory collapse and died during the study. The value "20 mm Hg" was selected to avoid enrollment of a pediatric population with LVD such that they would be most likely at-risk for these SAEs.

[0062] SAEs were collected from the start of study treatment until hospital discharge or 12 hours, whichever occurred sooner. Three SAEs were reported during the study period, and a total of 7 SAEs were reported. Three of these were fatal SAEs and 4 were nonfatal (one of which led to study discontinuation). In addition, one non-serious AE also lead to

discontinuation. A list of subjects who died, discontinued or experienced an SAE is provided in Table 5 below.

Table 5: Subjects that died, discontinued or experienced SAEs

Patient number	AE	Serious?	Fatal?	Discontinued treatment?
01020	Desaturation (hypoxia)	No	No	Yes
02002	Pulmonary edema	Yes	No	No
04001	Hypotension and cardiac arrest	Yes	Yes	No
04003	Hypotension and ECG changes	Yes	No	Yes
04008	Hypotension and hypoxemia	Yes	Yes	No
05002	Hypoxia and bradycardia (also pulmonary edema)	Yes	Yes	No
07003	Cardiac arrest	Yes	No	No
17001	Hypoxia	Yes	No	No

[0063] Two of the 3 fatal SAEs were deemed related to therapy. All 4 non-fatal SAEs were also considered related to therapy. The numbers of patients and events were too small to determine whether risk for SAEs differed by treatment, diagnosis, age, gender or race. At least two patients developed signs of pulmonary edema (subjects 05002 and 02002). This is of interest because pulmonary edema has previously been reported with the use of iNO in patients with LVD, and may be related to decreasing PVRI and overfilling of the left atrium. (Hayward CS et al., 1996, Inhaled Nitric Oxide in Cardiac Failure: Vascular Versus Ventricular Effects, *J Cardiovascular Pharmacology* 27:80-85; Bocchi EA et al., 1994, Inhaled Nitric Oxide Leading to Pulmonary Edema in Stable Severe Heart Failure, *Am J Cardiology* 74:70-72; and, Semigran MJ et al., 1994, Hemodynamic Effects of Inhaled Nitric Oxide in Heart Failure, *J Am Coll Cardiology* 24:982-988).

[0064] Although the SAE rate is within range for this population, it appears that patients with the most elevated PCWP at baseline had a disproportionately high number of these events. (Bocchi EA et al., 1994; Semigran MJ et al., 1994).

[0065] In the INOT22 study, 10 of the total 134 patients had a baseline PCWP $\geq$ 18 mm Hg (7.5%), of which, 3 subjects (04001, 02002 and 04003) had a SAE or were prematurely discontinued from the study (30%) compared to 6.5% for the entire cohort.

[0066] Although there were very few significant AEs in the INOT22 study, these events are consistent with the expected physiologic changes in patients with severe LVD. The events also corroborate prior observations that iNO is rapidly acting, selective for the pulmonary vasculature, and well-tolerated in most patients. The actual incidence of acute LVD during acute ventricular failure (AVT) is unknown. However, it is reasonable to expect that a significant number of patients are at-risk for an increased incidence of SAEs upon iNO treatment based upon the nature of the underlying nature of the illness, i.e., pulmonary hypertension and cardiovascular disease more generally. Thus, it would be advantageous to have physicians identify these patients prior to beginning iNO treatment, so that the physicians are alerted to this possible outcome.

[0067] Benefits and Risks Conclusions. The INOT22 study was designed to demonstrate the physiologic effects of iNO in a well defined cohort of children (i.e., intended patient population) with pulmonary hypertension using a high concentration, 80 ppm, of iNO, i.e., one that would be expected to have the maximal pharmacodynamic effect. INOT22 was the largest and most rigorous pharmacodynamic study of iNO conducted to date, and it confirms a number of prior observations, such as iNO being rapidly acting, selective for the pulmonary vasculature, and well-tolerated in most patients.

[0068] It is also acknowledged that rapidly decreasing the PVR may be undesirable and even dangerous in patients with concomitant LVD. In the INOT22 study, the overall numbers of SAEs and fatal SAEs are within the expected range for patients with this degree of cardiopulmonary disease. The overall rate is 7/124 (5.6%), which is closely comparable to the rate of 6% recently reported in a very similar cohort of patients. (Taylor CJ et al., 2007, Risk of cardiac catheterization under anaesthesia in children with pulmonary hypertension, *Br J Anaesth* 98(5):657-61). Thus, the overall rate of SAEs would seem to be more closely related to the underlying severity of illness of the patients rather than to the treatments given during this study.

[0069] The INOT22 study results demonstrate that patients who had pre-existing LVD may experience an increased rate of SAEs (e.g., pulmonary edema). During the course of the study, the protocol was amended to exclude patients with a PCWP > 20 mmHg. The benefit/risk of using iNO in patients with clinically significant LVD should be evaluated on a case by case

basis. A reduction in left ventricular afterload may perhaps be applied to minimize the occurrence of pulmonary edema.

CLAIMS

We Claim:

1. A method of reducing one or more of an adverse event or a serious adverse event in an intended patient population in need of being treated with inhalation of nitric oxide comprising excluding from such treatment patients who have pre-existing left ventricular dysfunction.

2. The method of claim 1, wherein the patients further have a pulmonary capillary wedge pressure greater than 20 mm Hg.

3. The method of claim 1, wherein the treatment further comprises inhalation of oxygen .

4. The method of claim 1, wherein the treatment is delivered using a ventilator.

5. The method of claim 1, wherein the patients having pre-existing left ventricular dysfunction have one or more of a condition selected from diastolic dysfunction, hypertensive cardiomyopathy, systolic dysfunction, ischemic cardiomyopathy, viral cardiomyopathy, idiopathic cardiomyopathy, autoimmune disease related cardiomyopathy , drug-related cardiomyopathy, toxin-related cardiomyopathy, structural heart disease, valvular heart disease, congenital heart disease, idiopathic pulmonary arterial hypertension and pulmonary hypertension cardiomyopathy, or associations thereof.

6. The method of any one of claims 1-5, wherein the patient population comprises children.

7. The method of any one of claims 1-5, wherein the patient population comprises adults.

8. The method of claim 1, wherein the patients are at risk of an adverse event or serious the adverse event is selected from pulmonary edema, hypotension, cardiac arrest, electrocardiogram changes, hypoxemia, hypoxia and bradycardia, or, associations thereof.

9. A method of reducing the risk or preventing the occurrence, in a human patient, of one or more of adverse events or serious adverse events associated with a medical treatment comprising inhalation of nitric oxide, said method comprising:

a. identifying a human patient eligible for inhalation of nitric oxide treatment;

b. determining if said patient has pre-existing left ventricular dysfunction; and

c. administering said medical treatment if said patient does not have pre-existing left ventricular dysfunction;

thereby reducing the risk or preventing the occurrence of the adverse event or serious adverse event associated with said medical treatment.

10. The method of claim 9, wherein said patient further exhibits a pulmonary capillary wedge pressure greater than 20 mm Hg.

11. The method of claims 9 or 10, wherein the patients who have pre-existing left ventricular dysfunction have one or more conditions selected from diastolic dysfunction, hypertensive cardiomyopathy, systolic dysfunction, ischemic cardiomyopathy, viral cardiomyopathy, idiopathic cardiomyopathy, autoimmune disease related cardiomyopathy, side effects due to drug-related cardiomyopathy, side effects due to toxin-related cardiomyopathy, structural heart disease, valvular heart disease, congenital heart disease, idiopathic pulmonary arterial hypertension, pulmonary hypertension and cardiomyopathy, or associations thereof.

12. The method of claim 9, wherein the medical treatment further comprises inhalation of oxygen.

13. The method of claim 9, wherein the treatment is delivered using a ventilator.

14. The method of claim 9, wherein the patient is a child.

15. The method of claim 9, wherein the patient is an adult.

16. A method of reducing the risk or preventing the occurrence, in a human patient, of one or more adverse events or a serious adverse events associated with a medical treatment comprising inhalation of nitric oxide, said method comprising:

a. providing pharmaceutically acceptable nitric oxide gas to a medical provider; and,

b. informing the medical provider that excluding human patients who have pre-existing left ventricular dysfunction from said treatment reduces the risk or prevents the occurrence of the adverse event or serious adverse event associated with said medical treatment.

17. The method of claim 16, wherein the patient is a child.

18. The method of claim 16, wherein the patient is an adult.

19. The method of claim 16, wherein the adverse event or serious adverse event is one or more of pulmonary edema, hypotension, cardiac arrest, electrocardiogram changes, hypoxemia, hypoxia and bradycardia, or, associations thereof.

20. A method of reducing the risk or preventing the occurrence, in a human patient, of one or more of adverse events or a serious adverse events associated with a medical treatment comprising inhalation of nitric oxide, said method comprising:

a. providing pharmaceutically acceptable nitric oxide gas to a medical provider; and,

b. informing the medical provider that human patients having preexisting left ventricular dysfunction experience an increased rate of serious adverse events associated with said medical treatment.

21. The method of claim 20, further comprising informing the medical provider of a risk of an adverse event or a serious adverse event in human patients who have a pulmonary capillary wedge pressure greater than 20 mm Hg.

22. The method of claim 20, further comprising informing the medical provider that there is a risk associated with using inhaled nitric oxides in human patients who have preexisting or clinically significant left ventricular dysfunction and that such risk should be evaluated on a case by case basis.

23. The method of claim 20, further comprising informing the medical provider that there is a risk associated with using inhaled nitric oxide in human patients who have left ventricular dysfunction.

24. A method of reducing one or more adverse events or serious adverse events in an intended patient population in need of being treated with iNO comprising:

a. identifying a patient eligible for iNO treatment;

b. evaluating and screening the patient to identify if the patient has pre-existing left ventricular dysfunction; and

c. excluding from iNO treatment a patient identified as having pre-existing left ventricular dysfunction.

25. A method of reducing the risk or preventing the occurrence, in a patient, of one or more adverse events or serious adverse events associated with a medical treatment comprising inhalation of nitric oxide, the method comprising:

a. identifying a patient in need of receiving inhalation of nitric oxide treatment;

b. evaluating and screening the patient to identify if the patient has pre-existing left ventricular dysfunction; and

c. administering the inhalation of nitric oxide if the patient does not have pre-existing left ventricular dysfunction, thereby reducing the risk or preventing the occurrence of the adverse event or significant adverse event associated with the inhalation of nitric oxide treatment.

26. The method of claims 24 or 25, wherein the patient having pre-existing left ventricular dysfunction exhibits a pulmonary capillary wedge pressure greater than 20 mm Hg.

27. The method of claim 1, wherein the intended patient population in need of being treated with the inhalation of nitric oxide has one or more of idiopathic pulmonary arterial hypertension characterized by PAPm > 25 mm Hg at rest, PCWP $\leq$ 15 mm Hg, and, a PVRI > 3 u·m^2; congenital heart disease with pulmonary hypertension repaired and unrepaired characterized by PAPm > 25 mm Hg at rest and PVRI > 3 u·m^2; cardiomyopathy characterized by PAPm > 25 mm Hg at rest and PVRI > 3 u·m^2; or, the patient is scheduled to undergo right heart catheterization to assess pulmonary vasoreactivity by acute pulmonary vasodilation testing.

28. The method of claim 1, 9, 16, 20, 24 or 25, further comprising reducing left ventricular afterload to minimize or reduce the risk of the occurrence of an adverse event or serious adverse event being pulmonary edema in the patient.

29. The method of claim 28, wherein the left ventricular afterload is minimized or reduced by administering a pharmaceutical dosage form comprising nitroglycerin or calcium channel blocker to the patient.

30. The method of claim 28, wherein the left ventricular afterload is minimized or reduced using an intra-aortic balloon pump.

ABSTRACT

The invention relates methods of reducing the risk or preventing the occurrence of an adverse event (AE) or a serious adverse event (SAE) associated with a medical treatment comprising inhalation of nitric oxide.

Electronic Patent Application Fee Transmittal

Application Number:	
Filing Date:	
Title of Invention:	Methods of Treating Term and Near-Term Neonates Having Hypoxic Respiratory Failure Associated with Clinical or Echocardiographic Evidence of Pulmonary Hypertension
First Named Inventor/Applicant Name:	James S. Baldassarre
Filer:	Janis K. Fraser/Christine Grace
Attorney Docket Number:	26047-0003011

Filed as Small Entity

Track I Prioritized Examination - Nonprovisional Application under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Utility filing Fee (Electronic filing)	4011	1	70	70
Utility Search Fee	2111	1	300	300
Utility Examination Fee	2311	1	360	360
Request for Prioritized Examination	2817	1	2000	2000
Pages:				
Claims:				
Miscellaneous-Filing:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Publ. Fee- Early, Voluntary, or Normal	1504	1	0	0
PROCESSING FEE, EXCEPT PROV. APPLS.	2830	1	70	70
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Miscellaneous:				
		Total in USD ($)		**2800**

Electronic Acknowledgement Receipt

EFS ID:	19803037
Application Number:	14454373
International Application Number:	
Confirmation Number:	3860
Title of Invention:	Methods of Treating Term and Near-Term Neonates Having Hypoxic Respiratory Failure Associated with Clinical or Echocardiographic Evidence of Pulmonary Hypertension
First Named Inventor/Applicant Name:	James S. Baldassarre
Customer Number:	94169
Filer:	Janis K. Fraser/Renee Neuman
Filer Authorized By:	Janis K. Fraser
Attorney Docket Number:	26047-0003011
Receipt Date:	07-AUG-2014
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Application Type:	Utility under 35 USC 111(a)

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File Listing:

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

1	TrackOne Request	Track.pdf	160498 6b8f08011feee0f9e03c229a17e5d726affeb653	no	2
Warnings:					
Information:					
2	Transmittal Letter	IDS.pdf	65337 d07cea110e1e4abf2d509b321b3be2c5bac63f96	no	2
Warnings:					
Information:					
3	Information Disclosure Statement (IDS) Form (SB08)	23271004.pdf	616505 b49e1163b4d2dd656b55c0e59dfd1a9dceaa7ea8	no	10
Warnings:					
Information:					
4	Power of Attorney	POA.pdf	191666 0f272a706786efb93fa958415521c63ba73ac2f8	no	3
Warnings:					
Information:					
5	Oath or Declaration filed	Declaration.pdf	111812 f4c42defa1bea780688d0b4cf07bdd1a1fab5205	no	2
Warnings:					
Information:					
6	Transmittal of New Application	Transmittal.pdf	98643 6156367f75a2e8cabb8b77252b15224a94023e17	no	3
Warnings:					
Information:					
7	Application Data Sheet	ADS.pdf	1561779 32b5d06c666aaffb7ca1fa42df2fc000ff78d190	no	8
Warnings:					
Information:					
8		Application.pdf	3048740 e75b44c4da15a405c10ef8fc42e4920ba8622426	yes	29

Multipart Description/PDF files in .zip description

Document Description	Start	End
Specification	1	22
Claims	23	28

	Abstract		29	29	
Warnings:					
Information:					
9	Fee Worksheet (SB06)	fee-info.pdf	40541 36d9bf4b373f9f577cf10e936818cae426f6a8f5	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	5895521		

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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.

Doc Code: TRACK1.REQ
Document Description: TrackOne Request

PTO/AIA/424 (03-14)

CERTIFICATION AND REQUEST FOR PRIORITIZED EXAMINATION UNDER 37 CFR 1.102(e) (Page 1 of 1)

First Named Inventor:	James S. Baldassarre	Non provisional Application Number (if known):	
Title of Invention:	Methods of Treating Term and Near-Term Neonates Having Hypoxic Respiratory Failure Associated with Clinical or Echocardiographic Evidence of Pulmonary Hypertension		

APPLICANT HEREBY CERTIFIES THE FOLLOWING AND REQUESTS PRIORITIZED EXAMINATION FOR THE ABOVE-IDENTIFIED APPLICATION.

1. The processing fee set forth in 37 CFR 1.17(i)(1), the prioritized examination fee set forth in 37 CFR 1.17(c), and if not already paid, the publication fee set forth in 37 CFR 1.18(d) have been filed with the request. The basic filing fee, search fee, and examination fee are filed with the request or have been already been paid. I understand that any required excess claims fees or application size fee must be paid for the application.

2. I understand that the application may not contain, or be amended to contain, more than four independent claims, more than thirty total claims, or any multiple dependent claims.

3. The applicable box is checked below:

I. ☒ Original Application (Track One) - Prioritized Examination under § 1.102(e)(1)

i. (a) The application is an original non provisional utility application filed under 35 U.S.C. 111(a). This certification and request is being filed with the utility application via EFS-Web.

---OR---

(b) The application is an original non provisional plant application filed under 35 U.S.C. 111(a). This certification and request is being filed with the plant application in paper.

ii. An executed inventor's oath or declaration under 37 CFR 1.63 or 37 CFR 1.64 for each inventor, **or** the application data sheet meeting the conditions specified in 37 CFR 1.53(f)(3)(i) is filed with the application.

II. ☐ Request for Continued Examination - Prioritized Examination under § 1.102(e)(2)

i. A request for continued examination has been filed with, or prior to, this form.
ii. If the application is a utility application, this certification and request is being filed via EFS-Web.
iii. The application is an original non provisional utility application filed under 35 U.S.C. 111(a), or is a national stage entry under 35 U.S.C. 371.
iv. This certification and request is being filed prior to the mailing of a first Office action responsive to the request for continued examination.
v. No prior request for continued examination has been granted prioritized examination status under 37 CFR 1.102(e)(2).

Signature /Janis K. Fraser/	Date August 7, 2014
Name (Print/Typed) Janis K. Fraser, Ph.D., J.D.	Practitioner Registration Number 34,819

Note: *This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4(d) for signature requirements and certifications. Submit multiple forms if more than one signature is required.**

☒ *Total of 1 forms are submitted.

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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 inspection or an issued patent.
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Named Inventor	:	James S. Baldassarre
Serial No.	:	Not Yet Assigned
Filed	:	Herewith
Title	:	METHODS OF TREATING TERM AND NEAR-TERM NEONATES HAVING HYPOXIC RESPIRATORY FAILURE ASSOCIATED WITH CLINICAL OR ECHOCARDIOGRAPHIC EVIDENCE OF PULMONARY HYPERTENSION

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

INFORMATION DISCLOSURE STATEMENT

Please consider the references listed on the enclosed PTO-SB-08 Form. Under 35 USC §120, this application relies on the earlier filing date of application serial numbers 12/494,598, filed on June 30, 2009; 12/820,866, filed on June 22, 2010; 12/821,041, filed on June 22, 2010; 13/651,660, filed on October 15, 2012; 13/683,417, filed on November 21, 2012; 13/683,444, filed on November 21, 2012; and 14/451,057, filed on August 4, 2014. The cited references were submitted to and/or cited by the Office in the prior applications and therefore are not provided in this application.

Applicant wishes to bring to the Examiner's attention the following related U.S. applications:

- USSN 12/494,598, filed June 30, 2009, abandoned (attorney docket no. 26047-0003001);
- USSN 12/820,866, filed June 22, 2010, abandoned (attorney docket no. 26047-0003002);
- USSN 12/820,980, filed June 22, 2010, abandoned (attorney docket no. 26047-0003003);
- USSN 12/821,020, filed June 22, 2010, Patent No. 8,282,966 (attorney docket no. 26047-0003004);
- USSN 12/821,041, filed June 22, 2010, Patent No. 8,293,284 (attorney docket no. 26047-0003005);
- USSN 13/683,236, filed November 21, 2012 (attorney docket no. 26047-0003006);
- USSN 13/651,660, filed October 15, 2012, Patent No. 8,431,163 (attorney docket no. 26047-0003007);

- USSN 13/683,417, filed November 21, 2012, Patent No. 8,795,741 (attorney docket no. 26047-0003008);
- USSN 13/683,444, filed November 21, 2012 (attorney docket no. 26047-0003009); and
- USSN 14/451,057, filed August 4, 2014 (attorney docket no. 26047-0003010).

The prosecution histories for these applications are available on PAIR, and thus are not provided with this communication. Copies of the prosecution history documents will be supplied if the Examiner requests.

This statement is being filed with the application. Apply any necessary charges or credits to Deposit Account 06-1050, referencing the above attorney docket number.

Respectfully submitted,

Date: August 7, 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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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99**)		
	Application Number	
	Filing Date	
	First Named Inventor	Baldassarre
	Art Unit	
	Examiner Name	
	Attorney Docket Number	26047-0003011

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	2	5651358	A	1997-07-29	Briend	
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	4	6063407	A	2000-05-16	Zapol	
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	First Named Inventor	Baldassarre
	Art Unit	
	Examiner Name	
	Attorney Docket Number	26047-0003011

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	20020185126	A1	2002-12-12	Krebs	
	2	20030131848	A1	2003-07-17	Stenzler	
	3	20040106954	A1	2004-06-03	Whitehurst	
	4	20090018136	A1	2009-01-15	Oppenheimer	
	5	20090029371	A1	2009-01-29	Elliott	
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	1	EP1682672	EP		2006-07-26			☐

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	Examiner Name	
	Attorney Docket Number	26047-0003011

	2	WO2005004884	WO		2005-01-20			☐
	3	WO2006127907	WO		2006-11-30			☐
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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.	T5
	1	Adatia et al., "Inhaled Nitric Oxide and Hemodynamic Evaluation of Patients With Pulmonary Hyptertension Before Transplantation," Journal of the American College of Cardiology, Elsevier, New York, NY, Vol. 25, No. 7, page 1663, June 1, 1995	☐
	2	Advances in Pulmonary Hypertension, Vol. 7(4), pages 1-418, Winter 2008-2009 (entire issue)	☐
	3	Al-Alaiyan et al., "Inhaled nitric oxide in persistent pulmonary hypertension of the newborn refractory to high-frequency ventilation," Crit. Care, Vol. 3, No. 1, pages 7-10 (1999)	☐
	4	Argenziano et al., "Inhaled Nitric Oxide is not a Myocardial Depressant in a Porcine Model of Heart Failure," The Journal of Thoracic and Cardiovascular Surgery, Vol. 115, pages 700-704 (1998)	☐
	5	Atz et al., "Combined Effects of Nitric Oxide and Oxygen During Acute Pulmonary Vasodilator Testing," Journal of the American College of Cardiology (JACC), Vol. 33, No. 3, pages 813-819 (1999)	☐
	6	Atz et al., "Inhaled nitric oxide in the neonate with cardiac disease," Seminars in Perinatology, Vol. 21(5), pages 441-455 (1997)	☐

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	Examiner Name	
	Attorney Docket Number	26047-0003011

	7	AU 2009202685 Office Action dated 06/17/10 (3 pages)	☐
	8	AU 2009202685 Office Action Response dated 07/29/2010, 19 pages	☐
	9	Azeka et al., "Effects of Low Doses of Inhaled Nitric Oxide Combined with Oxygen for the Evaluation of Pulmonary Vascular Reactivity in Patients with Pulmonary Hypertension," Pedatric Cardiol., Vol. 23, pages 20-26 (2002)	☐
	10	Barrington et al., "Inhaled Nitric Oxide for Preterm Infants: A Systematic Review," Pediatrics, Vol. 120; pages 1088-1099, DOI: 10.1542/peds (2007)	☐
	11	Barst et al., "Nitric Oxide in Combination with Oxygen versus Either Oxygen Alone or Nitric Oxide Alone for Acute Vasodilator Testing in Children with Pulmonary Hypertension: A Multicenter, Randomized Study," INO Therapeutics/ Ikaria, Baltimore Convention Center, May 3, 2009, 2 pages, Abstract, downloaded 7/2/2009 from http://127.0.0.1:9080/ PAS09A1/view.y?nu=PAS09L1_1507	☐
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	18	Bichel et al., "Successful weaning from cardiopulmonary bypass after cardiac surgery using inhaled nitric oxide", Pediatric Anaesthesia, Vol. 7, pages 335-339 (1997)	☐
	19	Bin-Nun et al., "Role of iNO in the modulation of pulmonary vascular resistance," Journal of Perinatology, Vol. 28, pages S84-S92 (2008)	☐
	20	Bland, "Pulmonary vascular dysfuction in preterm lambs with chronic lung disease," Am J Physical Lung Cell Mol. Physiol., Vol. 285: L76-L85 (2003)	☐
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	22	Bocchi et al.,"Inhaled Nitric Oxide Leading to Pulmonary Edema in Stable Severe Heart Failure," The American Journal of Cardiology, Vol. 74, pages 70-72 (1994)	☐
	23	Bolooki, Clinical Application of the Intra-Aortic Balloon Pump, 3rd Ed., pages 252-253 (1998)	☐
	24	Branson, "Inhaled Nitric Oxide in Adults," The Science Journal of the American Association for Respiratory Care 1997 Open Forum Abstracts, December 7, 1997, 2 pages, retrieved at <<http://www.rcjournal.com/abstracts/1997/?id=A00000929>> on 12/22/2010	☐
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	26	Bublik et al., "Pediatric cardiomyopathy as a chronic disease: A perspective on comprehensive care programs, Progress in Pediatric," Pediatric Cardiology, Vol. 25, pages 103-111 (2008)	☐
	27	Budts et al., "Residual pulmonary vasoreactivity to inhaled nitric oxide in patients with severe obstructive pulmonary hypertension and Eisenmenger syndrome," Heart, Vol. 86, pages 553-558 (2001)	☐
	28	Canadian Office Action mailed May 31, 2011 for Canadian Patent Application No. 2671029, a counterpart foreign application of US application no. 12/494,598	☐

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	29	Clark et al., "Low-Dose Nitric Oxide Therapy for Persistent Pulmonary Hypertension: 1-Year Follow-up," Journal of Perinatology, Vol. 23, pages 300-303 (2003)	☐
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	33	Cornfield et al., "Randomized, Controlled Trial of Low-dose Inhaled Nitric Oxide in the Treatment of Term and Near-term Infants With Respiratory Failure and Pulmonary Hypertension," Pediatrics, Vol. 104, No. 5, pages 1089-1094 (1999)	☐
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	36	Cuthbertson et al., "UK guidelines for the use of inhaled nitric oxide therapy in adults ICUs," Intensive Care Med., Vol. 23, Springer-Verlag, pages 1212-1218 (1997)	☐
	37	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)	☐
	38	Davidson et al., "Safety of Withdrawing Inhaled Nitric Oxide Therapy in Persistent Pulmonary Hypertension of the Newborn," Pediatrics, Vol. 104, No. 2, pages 231-236 (1999)	☐
	39	Day et al., "Pulmonary Vasodilatory Effects of 12 and 60 Parts Per Million Inhaled Nitric Oxide in Children with Ventricular Septal Defect," The American Journal of Cardiology, Vol. 75, pages 196-198 (1995)	☐

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	40	Definition of Contraindication on Medicine.net.com; http://www.medterms.com/script/main/art.asp?articlekey=17824; retrieved 3/14/2011; 2 pages	☐
	41	Delivery of Inhaled Nitric Oxide Therapy through an Adult or Pediatric Nasal Cannula, Reference: UTMB RESPIRATORY CARE SERVICES Reviewed: 05/31/05	☐
	42	Dickstein et al., "A Theoretic Analysis of the Effect of Pulmonary Vasodilation on Pulmonary Venous Pressure: Implications for Inhaled Nitric Oxide Therapy," The Journal of Heart and Lung Transplant, pages 715-721 (1996)	☐
	43	Dorland, "The American Illustrated Medical Dictionary," 7th edition, W.B. Saunders Company, page 113 (1914)	☐
	44	Dorling, "Neurodevelopmental outcome following Nitric Oxide Therapy for Persistent Pulmonary Hypertension in Term Newborn Infants," Neonatal Intensive Care Unit, Leicester Royal Infirmary, 8/8/2003, modified 11/12/2003, 3 pages	☐
	45	Douwes et al., "The Maze of Vasodilator Response Criteria," Published online: 26 November 2010, Pediatr. Cardiol., Vol. 32, pages 245-246 (2011)	☐
	46	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)	☐
	47	http://www.cc.nih.gov/ccmd/clinical_services.html, page last updated May 19, 2011	☐
	48	http://www.medterms.com/script/main/art.asp?articlekey=17824, Definition of Contraindication, last Editorial Review March 19, 2012	☐
	49	Elbl et al., "Long-term serial echocardiographic examination of late anthracycline cardiotoxicity and its prevention by dexrazoxane in paediatric patients," Eur. J. Pediatr., Vol. 164, pages 678-684 (2005)	☐
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	Application Number	
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	First Named Inventor	Baldassarre
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	Attorney Docket Number	26047-0003011

CERTIFICATION STATEMENT

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

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Signature	/Janis K. Fraser/	Date (YYYY-MM-DD)	2014-08-07
Name/Print	Janis K. Fraser	Registration Number	34819

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Application Number	Not Yet Assigned
Filing Date	Herewith
First Named Inventor	James S. Baldassarre
Title	METHODS OF TREATING TERM AND NEAR-TERM NEONATES HAVING HYPOXIC RESPIRATORY FAILURE ASSOCIATED WITH CLINICAL OR ECHOCARDIOGRAPHIC EVIDENCE OF PULMONARY HYPERTENSION
Art Unit	
Examiner Name	
Attorney Docket Number	26047-0003011

SIGNATURE of Applicant or Patent Practitioner

Signature	/Janis K. Fraser/	Date (Optional)	August 7, 2014
Name	Janis K. Fraser, Ph.D., J.D.	Registration Number	34,819
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NOTE: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4(d) for signature requirements and certifications. If more than one applicant, use multiple forms.

☒ *Total of 1 forms are submitted.

This collection of information is required by 37 CFR 1.131, 1.32, and 1.33. 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 1.11 and 1.14. This collection is estimated to take 3 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, 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.**
23270815.doc

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

PTO/AIA/82B(07-13)
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POWER OF ATTORNEY BY APPLICANT

I hereby revoke all previous powers of attorney given in the application identified in either the attached transmittal letter or the boxes below.

Application Number	Filing Date

(Note: The boxes above may be left blank if information is provided on form PTO/AIA/82A.)

☒ I hereby appoint the Patent Practitioner(s) associated with the following Customer Number as my/our attorney(s) or agent(s), and to transact all business in the United States Patent and Trademark Office connected therewith for the application referenced in the attached transmittal letter (form PTO/AIA/82A) or identified above:

94169

OR

☐ I hereby appoint Practitioner(s) named in the attached list (form PTO/AIA/82C) as my/our attorney(s) or agent(s), and to transact all business in the United States Patent and Trademark Office connected therewith for the patent application referenced in the attached transmittal letter (form PTO/AIA/82A) or identified above. (Note: Complete form PTO/AIA/82C.)

Please recognize or change the correspondence address for the application identified in the attached transmittal letter to:

☐ The address associated with the above-mentioned Customer Number

OR

☒ The address associated with Customer Number: **94169**

OR

Firm or Individual Name					
Address					
City		State		Zip	
Country					
Telephone		Email			

I am the Applicant (if the Applicant is a juristic entity, list the Applicant name in the box):

INO Therapeutics LLC

☐ Inventor or Joint Inventor (title not required below)

☐ Legal Representative of a Deceased or Legally Incapacitated Inventor (title not required below)

☒ Assignee or Person to Whom the Inventor is Under an Obligation to Assign (provide signer's title if applicant is a juristic entity)

☐ Person Who Otherwise Shows Sufficient Proprietary Interest (e.g., a petition under 37 CFR 1.46(b)(2) was granted in the application or is concurrently being filed with this document) (provide signer's title if applicant is a juristic entity)

SIGNATURE of Applicant for Patent

The undersigned (whose title is supplied below) is authorized to act on behalf of the applicant (e.g., where the applicant is a juristic entity).

Signature	William Scheinler	Date (Optional)	7/21/14
Name	William Scheinler		
Title	Associate General Counsel		

NOTE: Signature - This form must be signed by the applicant in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications. If more than one applicant, use multiple forms.

☒ *Total of 1 forms are submitted.

PTO/AIA/82C (07-13)
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POWER OF ATTORNEY BY APPLICANT

No more than ten (10) patent practitioners total may be appointed as set forth below by name and registration number. This page need not be submitted if appointing the Patent Practitioner(s) associated with a Customer Number (see form PTO/AIA/82B):

Name	Registration Number

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Named Inventor	:	James S. Baldassarre
Serial No.	:	Not Yet Assigned
Filed	:	Herewith
Title	:	METHODS OF TREATING TERM AND NEAR-TERM NEONATES HAVING HYPOXIC RESPIRATORY FAILURE ASSOCIATED WITH CLINICAL OR ECHOCARDIOGRAPHIC EVIDENCE OF PULMONARY HYPERTENSION

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

SUBMISSION OF DECLARATION

The attached declaration of inventor James S. Baldassarre is a copy of his declaration filed in a parent application, U.S. serial no. 14/451,057. The present application is a continuation of U.S. serial no. 14/451,057.

Respectfully submitted,

Date: August 7, 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

23270592.doc

Attorney Docket No. 26047-0003007

PTO/AIA/01 (06-12)
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DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76)

Title of Invention	METHODS OF REDUCING THE RISK OF OCCURRENCE OF PULMONARY EDEMA ASSOCIATED WITH INHALATION OF NITRIC OXIDE GAS

As the below named inventor, I hereby declare that:

This declaration is directed to:

☒ The attached application, or

☐ United States application or PCT international application number _____

filed on _____

The above-identified application was made or authorized to be made by me.

I believe that I am the original inventor or an original joint inventor of a claimed invention in the application.

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

WARNING:

Petitioner/applicant is cautioned to avoid submitting personal information in documents filed in a patent application that may contribute to identity theft. Personal information such as social security numbers, bank account numbers, or credit card numbers (other than a check or credit card authorization form PTO-2038 submitted for payment purposes) is never required by the USPTO to support a petition or an application. If this type of personal information is included in documents submitted to the USPTO, petitioners/applicants should consider redacting such personal information from the documents before submitting them to the USPTO. Petitioner/applicant is advised that the record of a patent application is available to the public after publication of the application (unless a non-publication request in compliance with 37 CFR 1.213(a) is made in the application) or issuance of a patent. Furthermore, the record from an abandoned application may also be available to the public if the application is referenced in a published application or an issued patent (see 37 CFR 1.14). Checks and credit card authorization forms PTO-2038 submitted for payment purposes are not retained in the application file and therefore are not publicly available.

LEGAL NAME OF INVENTOR

Inventor: James S. Baldassarre Date (Optional): October 8, 2012

Signature: /James S. Baldassarre/

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form. Use an additional PTO/AIA/01 form for each additional inventor.

PTO/SB/06 (09-11)
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PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number	Filing Date	☐ To be Mailed
14/454,373	08/07/2014	

ENTITY: ☐ LARGE ☒ SMALL ☐ MICRO

APPLICATION AS FILED – PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	RATE ($)	FEE ($)
☒ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	**70**
☒ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A	**300**
☒ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	**360**
TOTAL CLAIMS (37 CFR 1.16(i))	30 minus 20 =	* 10	x $40 =	**400**
INDEPENDENT CLAIMS (37 CFR 1.16(h))	4 minus 3 =	* 1	x $210 =	**210**
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).			
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))				
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL	**1340**

APPLICATION AS AMENDED – PART II

AMENDMENT

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	*	Minus	**	=	x $ =	
Independent (37 CFR 1.16(h))	*	Minus	***	=	x $ =	
☐ Application Size Fee (37 CFR 1.16(s))						
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
					TOTAL ADD'L FEE	

AMENDMENT

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	*	Minus	**	=	x $ =	
Independent (37 CFR 1.16(h))	*	Minus	***	=	x $ =	
☐ Application Size Fee (37 CFR 1.16(s))						
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
					TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".

*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".

The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

LDRC
/EVA GILLIS/