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November 21, 2012

Attorney Docket No.: 26047-0003008/3000-US-0008CON6

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This application is a continuation of U.S. Application Serial No. 12/820,866, filed June 22, 2010, which is a continuation of U.S. Serial No. 12/494,598, filed June 30, 2009, and now abandoned. This application is also a continuation of U.S. Serial No. 13/651,660, 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.

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Title: METHODS FOR TREATING PATIENTS WHO ARE CANDIDATES FOR INHALED NITRIC OXIDE TREATMENT

Assignee: INO Therapeutics LLC

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	7
Abstract	1
Declarations (2), with cover sheet	3

Enclosures:

Certification and Request for Prioritized Examination (Track I) (1 page)
Application Data Sheet (6 pages)
Power of Attorney to Prosecute Applications Before the USPTO (1 page) together with Statement Under 37 CFR 3.73 (c) (2 pages) and copies of 3 assignments (James S. Baldassarre and Ralf Rosskamp to Ikaria Holdings, Inc.; Ikaria Holdings, Inc. to Ikaria, Inc.; and Ikaria, Inc. to INO Therapeutics LLC) (83 pages)

	Total
Basic Filing fee	$390
Search fee	$620
Examination fee	$250
Publication fee	$300
Track I processing fee	$130
Track I prioritized examination fee	$4800
Application size fee for each 50 pages over 100	$0
Excess independent claim fee	$0
Excess claim fee	$620
Total Filing fee	$7110

The fees totaling $7110 are being paid concurrently herewith on the Electronic Filing System (EFS) by way of Deposit Account authorization. Apply all charges or credits to Deposit Account No. 06-1050, referencing Attorney Docket No. 26047-0003006.

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.

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METHODS FOR TREATING PATIENTS WHO ARE CANDIDATES FOR INHALED NITRIC OXIDE TREATMENT

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application is a continuation of U.S. Application Serial No. 12/820,866, filed June 22, 2010, which is a continuation of U.S. Serial No. 12/494,598, filed June 30, 2009, and now abandoned. This application is also a continuation of U.S. Serial No. 13/651,660, 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.

BACKGROUND OF THE INVENTION

[0002] 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.

[0003] 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

[0004] 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.

[0005] 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.

[0006] 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.

[0007] 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.

[0008] 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.

[0009] 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.

[0010] 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.

[0011] 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.

[0012] In an exemplary embodiment of the method, the patients having pre-existing LVD demonstrate a PCWP $\geq$ 20 mm Hg.

[0013] In another exemplary embodiment of the method, the iNO treatment further comprises inhalation of oxygen (O_2) or concurrent ventilation.

[0014] 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.

[0015] In another exemplary embodiment of the method, the patient population comprises children.

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

[0017] 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.

[0018] 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.

[0019] 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

[0020] 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 CONTRAINDICATIONS section of the prescribing information for INOmax® states that INOmax® should not be used in the treatment of neonates known to be dependent on right-to-left shunting of blood.

[0021] 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.

[0022] 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.

[0023] As used herein, the term "children" (and variations thereof) includes those being around 4 weeks to 18 years of age.

[0024] As used herein, the term "adult" (and variations thereof) includes those being over 18 years of age.

[0025] 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.

[0026] 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.

[0027] 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.

[0028] 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.

[0029] 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 a 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.

[0030] 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.

[0031] 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.

[0032] 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, 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.

[0033] 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.

[0034] 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.

[0035] 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).

[0036] 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.

[0037] The pivotal trials leading to the approval of INOmax® were the CINRGI and NINOS study.

[0038] 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).

[0039] 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
Death	5/89 (6%)	3/97 (3%)	0.48

[0040] Significantly fewer neonates in the ECMO group required ECMO, and INOmax® significantly improved oxygenation, as measured by PaO_2, OI, and alveolar-arterial gradient.

[0041] NINOS study. (See Inhaled Nitric Oxide in Full-Term and Nearly Full-Term Infants with Hypoxic Respiratory Failure; NEJM, Vol. 336, No. 9, 597).

[0042] 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

[0043] 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.

[0044] In both the NINOS and CINRGI studies, the duration of hospitalization was similar in INOmax® and placebo-treated groups.

[0045] 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.

[0046] 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.

[0047] 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%)

[0048] 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.

[0049] 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

[0050] 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).

[0051] 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.

[0052] 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 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.

[0053] 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.

[0054] 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)

[0055] 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)

[0056] 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)

[0057] 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.

[0058] 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.

[0059] 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.

[0060] 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.

[0061] 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 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

[0062] 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).

[0063] 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).

[0064] 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.

[0065] 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.

[0066] 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.

[0067] 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.

[0068] 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.

We claim:

1. A method of treating patients who are candidates for inhaled nitric oxide treatment, which method reduces the risk that inhalation of nitric oxide gas will induce an increase in pulmonary capillary wedge pressure (PCWP) leading to pulmonary edema in neonatal patients with hypoxic respiratory failure, the method comprising:

(a) performing at least one diagnostic process to identify a plurality of term or near-term neonatal patients who have hypoxic respiratory failure and are candidates for 20 ppm inhaled nitric oxide treatment, wherein the patients are not dependent on right-to-left shunting of blood;

(b) determining that a first patient of the plurality does not have left ventricular dysfunction;

(c) determining that a second patient of the plurality has left ventricular dysfunction, so is at particular risk of increased PCWP leading to pulmonary edema upon treatment with inhaled nitric oxide;

(d) administering 20 ppm inhaled nitric oxide treatment to the first patient; and

(e) excluding the second patient from treatment with inhaled nitric oxide, based on the determination that the second patient has left ventricular dysfunction, so is at particular risk of increased PCWP leading to pulmonary edema upon treatment with inhaled nitric oxide.

2. The method of claim 1, wherein the first patient has congenital heart disease.

3. The method of claim 1, wherein the left ventricular dysfunction of the second patient is attributable to congenital heart disease.

4. The method of claim 1, wherein the second patient is determined to be at particular risk not only of increased PCWP leading to pulmonary edema, but also of other serious adverse events, upon treatment with inhaled nitric oxide, and the second patient is excluded from inhaled nitric oxide treatment based on the determination that the second patient has left ventricular dysfunction and so is at particular risk not only of increased PCWP leading to pulmonary edema, but also other serious adverse events, upon treatment with inhaled nitric oxide.

5. The method of claim 4, wherein the left ventricular dysfunction of the second patient is attributable to congenital heart disease.

6. The method of claim 1, wherein determining that the first patient does not have pre-existing left ventricular dysfunction and the second patient does have pre-existing left ventricular dysfunction comprises performing at least one diagnostic process on each of the first and second patients.

7. The method of claim 1, wherein determining that the first patient does not have pre-existing left ventricular dysfunction and the second patient does have pre-existing left ventricular dysfunction comprises performing echocardiography on the first and second patients.

8. The method of claim 1, wherein the second patient has a PCWP that is greater than or equal to 20 mm Hg.

9. A method of treating patients who are candidates for inhaled nitric oxide treatment, which method reduces the risk that inhalation of the nitric oxide gas will induce an increase in PCWP leading to pulmonary edema in neonatal patients with hypoxic respiratory failure, said method comprising:

(a) performing at least one diagnostic process to identify a plurality of term or near-term neonatal patients who have hypoxic respiratory failure and are candidates for 20 ppm inhaled nitric oxide treatment, wherein the patients are not dependent on right-to-left shunting of blood;

(b) determining that a first patient of the plurality does not have left ventricular dysfunction;

(c) determining that a second patient of the plurality has left ventricular dysfunction, so is at particular risk of increased PCWP leading to pulmonary edema upon treatment with inhaled nitric oxide;

(d) administering 20 ppm inhaled nitric oxide treatment to the first patient; and

(e) excluding the second patient from treatment with inhaled nitric oxide based on the determination in (c), or, despite the second patient's ongoing need for inhaled nitric oxide treatment for hypoxic respiratory failure, discontinuing the second patient's treatment with

inhaled nitric oxide after it was begun, the discontinuation being in view of the determination in (c).

10. The method of claim 9, wherein the discontinuation is in view of both the determination in (c) and the second patient's experiencing an adverse event upon treatment with inhaled nitric oxide.

11. The method of claim 10, wherein the adverse event comprises pulmonary edema.

12. The method of claim 10, wherein the adverse event comprises at least one of increased PCWP, systemic hypotension, bradycardia, or cardiac arrest.

13. The method of claim 9, wherein (c) comprises determining that the second patient has a pulmonary capillary wedge pressure that is greater than or equal to 20 mm Hg.

14. The method of claim 9, wherein the first patient has congenital heart disease.

15. The method of claim 9, wherein the left ventricular dysfunction of the second patient is attributable to congenital heart disease.

16. The method of claim 14, wherein the left ventricular dysfunction of the second patient is attributable to congenital heart disease.

17. The method of claim 9, wherein

the second patient is determined to be at particular risk not only of increased PCWP leading to pulmonary edema, but also of other serious adverse events, upon treatment with inhaled nitric oxide; and

either (i) the second patient is excluded from inhaled nitric oxide treatment based on both the determination in (c) and the determination that the second patient is also at risk of other serious adverse events upon treatment with inhaled nitric oxide; or (ii) despite the second patient's ongoing need for inhaled nitric oxide treatment for hypoxic respiratory failure, the second patient's treatment with inhaled nitric oxide is discontinued after it was begun, the

discontinuation being in view of both the determination in (c) and the determination that the second patient is also at risk of other serious adverse events upon treatment with inhaled nitric oxide.

18. The method of claim 17, wherein the other serious adverse events comprise one or more of increased PCWP, systemic hypotension, bradycardia, or cardiac arrest.

19. The method of claim 17, wherein the discontinuation is in view of: the determination in (c), the determination that the second patient is also at risk of other serious adverse events, and the second patient's experiencing an adverse event upon treatment with inhaled nitric oxide.

20. The method of claim 19, wherein the adverse event experienced by the second patient comprises pulmonary edema.

21. The method of claim 19, wherein the adverse event experienced by the second patient comprises at least one of increased PCWP, systemic hypotension, bradycardia, or cardiac arrest.

22. The method of claim 9, wherein determining that the first patient does not have pre-existing left ventricular dysfunction and the second patient does have pre-existing left ventricular dysfunction comprises performing at least one diagnostic process on each of the first and second patients.

23. The method of claim 9, wherein determining that the first patient does not have pre-existing left ventricular dysfunction and the second patient does have pre-existing left ventricular dysfunction comprises performing echocardiography on each of the first and second patients.

24. A method of treating patients who are candidates for inhaled nitric oxide treatment, which method reduces the risk of inducing an increase in PCWP leading to pulmonary edema in neonatal patients with hypoxic respiratory failure, the method comprising:

(a) performing at least one diagnostic process to identify a plurality of term or near-term neonatal patients who have hypoxic respiratory failure and are candidates for 20 ppm inhaled nitric oxide treatment, wherein the patients are not dependent on right-to-left shunting of blood;

(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 increased PCWP leading to pulmonary edema upon treatment with inhaled nitric oxide; and

(e) 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.

25. The method of claim 24, wherein the second treatment regimen does not comprise administration of inhaled nitric oxide.

26. The method of claim 24, wherein the second treatment regimen comprises beginning administration of inhaled nitric oxide but discontinuing the administration upon determination that inhaling nitric oxide has increased the second patient's PCWP and/or induced pulmonary edema in the second patient.

27. The method of claim 24, wherein the first patient has congenital heart disease.

28. The method of claim 24, wherein the pre-existing left ventricular dysfunction of the second patient is attributable to congenital heart disease.

29. The method of claim 24, wherein the diagnostic process comprises echocardiography.

30. The method of claim 24, wherein the second patient has a pulmonary capillary wedge pressure that is greater than or equal to 20 mm Hg.

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 the patient, leading to pulmonary edema.

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Attorney Docket No. 26047-0003007

PTO/AIA/80 (07-12)

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SIGNATURE of Assignee of Record
The individual whose signature and title is supplied below is authorized to act on behalf of the assignee

Signature		Date	Sept 28, 2012
Name	Jonathan Provoost, Esq.	Telephone	908 238 6892
Title	Associate General Counsel		

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STATEMENT UNDER 37 CFR 3.73(c)

Applicant/Patent Owner: INO Therapeutics LLC

Application No./Patent No.: filed herewith Filed/Issue Date: _____

Titled: METHODS FOR TREATING PATIENTS WHO ARE CANDIDATES FOR INHALED NITRIC OXIDE TREATMENT

INO Therapeutics LLC, a corporation
(Name of Assignee) (Type of Assignee, e.g., corporation, partnership, university, government agency, etc.)

states that, for the patent application/patent identified above, it is (choose one of the option 1, 2, 3 or 4 below):

1. ☒ The assignee of the entire right, title, and interest.

2. ☐ An assignee of less than the entire right, title and interest (check applicable box):

☐ The extent (by percentage) of its ownership interest is _____. Additional Statement(s) by the owners holding the balance of the interest must be submitted to account for 100% of the ownership interest.

☐ There are unspecified percentages of ownership. The other parties, including inventors, who together own the entire right, title and interest are:

Additional Statement(s) by the owner(s) holding the balance of the interest must be submitted to account for the entire right, title, and interest.

3. ☐ The assignee of an undivided interest in the entirety (a complete assignment from one of the joint inventors was made). The other parties, including inventors, who together own the entire right, title, and interest are:

Additional Statement(s) by the owner(s) holding the balance of the interest must be submitted to account for the entire right, title, and interest.

4. ☐ The recipient, via a court proceeding or the like (e.g., bankruptcy, probate), of an undivided interest in the entirety (a complete transfer of ownership interest was made). The certified document(s) showing the transfer is attached.

The interest identified in option 1, 2 or 3 above (not option 4) is evidenced by either (choose one of the options A or B below):

A. ☐ An assignment from the inventor(s) of the patent application/patent identified above. The assignment was recorded in the United States Patent and Trademark Office at Reel _____, Frame _____, or for which a copy thereof is attached.

B. ☒ A chain of title from the inventor(s), of the patent application/patent identified above, to the current assignee as follows:

Inventors: James S. Baldassarre and Ralf Rosskamp

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[NOTE: A separate copy *(i.e.,* a true copy of the original assignment document(s)) must be submitted to Assignment Division in accordance with 37 CFR Part 3, to record the assignment in the records of the USPTO. See MPEP 302.08]

The undersigned (whose title is supplied below) is authorized to act on behalf of the assignee.

Janis Fraser — Nov 21, 2012
Signature — Date

Janis K. Fraser, Ph.D., J.D. — Attorney for assignee Reg. No. 34,819
Printed or Typed Name — Title

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Serial Number 12/494,598
Filing Date 6/30/2009
Inventorship ..... Baldassarre et al.
Applicant ..... James S. Baldassarre
Attorney's Docket No. .....I001-0002US (formerly 135197.00084)
Title: Methods of Treating Term and Near-Term Neonates Having Hypoxic Respiratory Failure Associated with Clinical or Echocardiographic Evidence of Pulmonary Hypertension

PATENT ASSIGNMENT

PARTIES TO THE ASSIGNMENT

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AGREEMENT

WHEREAS, ASSIGNORS (listed above) are inventors of an invention entitled "Methods of Treating Term and Near-Term Neonates Having Hypoxic Respiratory Failure Associated with Clinical or Echocardiographic Evidence of Pulmonary Hypertension" for which:

☐ a provisional application for United States Letters Patent was filed on _____ and was given U.S. Serial No. _____; and/or

☒ a non-provisional application for United States Letters Patent was:

☒ filed on 6/30/2009 and was given U.S. Serial No. 12/494,598; or filed concurrently herewith. Assignors hereby authorize and request ASSIGNEE's legal representatives, of Lee & Hayes, PLLC, 601 W Riverside Ave, Suite 1400, Spokane, Washington 99201, who are associated with customer number 29150, to insert in the caption above the serial number and filing date of the patent application when known.

WHEREAS Ikaria Holdings, Inc., (hereinafter referred to as ASSIGNEE), a corporation of the State of New Jersey having a place of business at 6 Route 173, Clinton, New Jersey 08809, is desirous of acquiring the entire right, title and interest in and to the invention and in and to any letters patent that may be granted therefore in the United States and in any and all foreign countries;

NOW, THEREFORE, in exchange for good and valuable consideration, the receipt of which is hereby acknowledged, ASSIGNORS hereby sell, assign and transfer unto ASSIGNEE, the entire right, title and interest in and to said invention, said application and any and all letters patent which may be granted for said invention in the United States of America and its territorial possessions and in any and all foreign countries, and in any and all divisions, reissues and continuations thereof, including the right to file foreign applications directly in the name of ASSIGNEE and to claim priority rights deriving from said United States application to which said foreign applications are entitled by virtue of international convention, treaty or otherwise, said invention, application and all letters patent on said invention to be held and enjoyed by ASSIGNEE and its successors and assigns for their use and benefit and of their successors and assigns as fully and entirely as the same would have been held and enjoyed by ASSIGNORS had this assignment, transfer and sale not been made. ASSIGNORS hereby authorize and request the Commissioner of Patents and Trademarks to issue all letters patent on said invention to ASSIGNEE. ASSIGNORS agree to execute all instruments and documents required for the making and prosecution of applications for United States and foreign letters patent on said invention, for litigation regarding said

letters patent, or for the purpose of protecting title to said invention or letters patent therefore.

Date: 8/31/09 By: James S. Baldassarre

Date: 9/8/09 By: Ralf Rosskamp

Daria Cooney 8/31/09

DARIA COONEY
NOTARY PUBLIC
WARREN COUNTY, NJ.
MY COMMISION EXPIRES 5-13-2013

DARIA COONEY 9/8/09
NOTARY PUBLIC
WARREN COUNTY, NJ.
MY COMMISION EXPIRES 5-13-2013

Delaware

The First State

I, JEFFREY W. BULLOCK, SECRETARY OF STATE OF THE STATE OF DELAWARE, DO HEREBY CERTIFY THE ATTACHED IS A TRUE AND CORRECT COPY OF THE RESTATED CERTIFICATE OF "IKARIA HOLDINGS, INC.", CHANGING ITS NAME FROM "IKARIA HOLDINGS, INC." TO "IKARIA, INC.", FILED IN THIS OFFICE ON THE SEVENTH DAY OF MAY, A.D. 2010, AT 12:36 O'CLOCK P.M.

A FILED COPY OF THIS CERTIFICATE HAS BEEN FORWARDED TO THE NEW CASTLE COUNTY RECORDER OF DEEDS.

Jeffrey W. Bullock, Secretary of State

4196771 8100

AUTHENTICATION: 7979373

100477026

DATE: 05-07-10

You may verify this certificate online at corp.delaware.gov/authver.shtml

State of Delaware
Secretary of State
Division of Corporations
Delivered 12:42 PM 05/07/2010
FILED 12:36 PM 05/07/2010
SRV 100477026 - 4196771 FILE

RESTATED
CERTIFICATE OF INCORPORATION
OF
IKARIA HOLDINGS, INC.
(Originally incorporated as ITL Holdings, Inc. on August 18, 2006)

ARTICLE I
NAME

The name of the Corporation is Ikaria, Inc. (the "Corporation").

ARTICLE II
REGISTERED OFFICE AND AGENT

The address of the Corporation's registered office in the State of Delaware is Corporation Service Company, 2711 Centerville Road, Suite 400, City of Wilmington 19808, County of New Castle. The name of its registered agent at such address is Corporation Service Company.

ARTICLE III
PURPOSE

The purpose of the Corporation is to engage in any lawful act or activity for which corporations may be organized under the Delaware General Corporation Law (the "DGCL").

ARTICLE IV
CAPITAL STOCK

The total number of shares of all classes of capital stock which the Corporation shall have authority to issue is two hundred thirteen million, four hundred two thousand, six hundred (213,402,600) shares, of which:

One hundred twenty five million (125,000,000) shares, par value $0.01 per share, shall be shares of common stock, of which one hundred ten million (110,000,000) shares shall be designated "Voting Common Stock" (the "Voting Common Stock") and fifteen million (15,000,000) shares shall be designated Non-Voting Common Stock" (the "Non-Voting Common Stock"); and

Eighty-eight million, four hundred two thousand, six hundred (88,402,600) shares, par value $0.01 per share, shall be shares of preferred stock (the "Preferred Stock"), of which eleven million, four hundred twenty-one thousand, three hundred (11,421,300) shares shall be designated "Series A Convertible Preferred Stock"; seventy-six million, nine hundred eighty thousand, nine hundred (76,980,900) shares shall be designated "Series B Convertible Preferred Stock"; one hundred (100) shares Shall be designated "Series C-1 Non-Convertible Preferred Stock"; one hundred (100) shares shall be designated

"Series C-2 Non-Convertible Preferred Stock"; one hundred (100) shares shall be designated "Series C-3 Non-Convertible Preferred Stock"; and one hundred (100) shares shall be designated "Series C-4 Non-Convertible Preferred Stock".

ARTICLE V
VOTING COMMON STOCK

SECTION 1. GENERAL.

Except as otherwise required by law or as expressly provided in this Certificate of Incorporation, each share of Voting Common Stock shall have the same powers, rights and privileges and shall rank equally, share ratably and be identical in all respects as to all matters, with each other share of Voting Common Stock and with each share of Non-Voting Common Stock.

SECTION 2. DIVIDENDS.

(a) Subject to the rights of the holders of Preferred Stock and to the other provisions of this Certificate of Incorporation, holders of Voting Common Stock and Non-Voting Common Stock shall be entitled to receive equally, on a per share basis, such dividends and other distributions in cash, securities or other property of the Corporation as may be declared thereon by the Board of Directors from time to time out of assets or funds of the Corporation legally available therefor.

(b) The Corporation shall not effect a subdivision, combination or reclassification of the outstanding shares of Voting Common Stock into a greater or lesser number of shares of Voting Common Stock unless a comparable adjustment is at the same time being made to the Non-Voting Common Stock.

SECTION 3. VOTING RIGHTS.

At every annual or special meeting of stockholders of the Corporation, each holder of Voting Common Stock shall be entitled to cast one vote for each share of Voting Common Stock standing in such holder's name on the stock transfer records of the Corporation; provided, however, that, except as otherwise required by law, holders of Voting Common Stock, as such, shall not be entitled to vote on any amendment to this Certificate of Incorporation (including any certificate of designation relating to any series of Preferred Stock) that relates solely to the terms of one or more outstanding series of Preferred Stock if the holders of such affected series are entitled to vote thereon, either separately or together with the holders of one or more other such series, pursuant to this Certificate of Incorporation (including pursuant to any certificate of designation relating to any series of Preferred Stock).

ARTICLE VI
NON-VOTING COMMON STOCK

SECTION 1. GENERAL.

Except as otherwise required by law or as expressly provided in this Certificate of Incorporation, each share of Non-Voting Common Stock shall have the same powers, rights and privileges and shall rank equally, share ratably and be identical in all respects as to all matters, with each other share or Non-Voting Common Stock and with each share of Voting Common Stock.

SECTION 2. DIVIDENDS.

Subject to the rights of the holders of Preferred Stock and to the other provisions of this Certificate of Incorporation, holders of Non-Voting Common Stock and Voting Common Stock shall be entitled to receive equally, on a per share basis, such dividends and other distributions in cash, securities or other property of the Corporation as may be declared thereon by the Board of Directors from time to time out of assets or funds of the Corporation legally available therefor.

SECTION 3. VOTING RIGHTS.

The holders of Non-Voting Common Stock shall not be entitled to any voting rights except as required by law.

SECTION 4. CONVERSION.

(a) In the event there shall occur an Initial Public Offering, then, immediately prior to the consummation of the Initial Public Offering, without any further action by the Corporation or the holders of shares of Non-Voting Common Stock, each outstanding share of Non-Voting Common Stock shall automatically be converted into one fully paid and non-assessable share of Voting Common Stock.

(b) The Corporation shall at all times reserve and keep available, free from liens, charges and security interests and not subject to any preemptive rights, for issuance upon conversion of the Non-Voting Common Stock, such number of its authorized but unissued shares of Voting Common Stock as will be sufficient to permit the conversion of all outstanding shares of Non-Voting Common Stock, and shall take or cause to be taken all action required to increase the authorized number of shares of Voting Common Stock if necessary to permit the conversion of all outstanding shares of Non-Voting Common Stock and to ensure that the shares of Voting Common Stock may be issued without violation of any applicable law or regulation or of any requirement of any securities exchange or inter-dealer quotation system on which the shares of Voting Common Stock may be listed or traded.

(c) The Corporation shall not effect a subdivision, combination or reclassification of the outstanding shares of Non-Voting Common Stock into a greater or lesser number of shares of Non-Voting Common Stock unless a comparable adjustment is at the same time being made to the Voting Common Stock.

ARTICLE VII
PREFERRED STOCK

The Board of Directors is authorized, subject to limitations prescribed by law, to provide by resolution or resolutions for the issuance of shares of Preferred Stock in one or more series, to establish the number of shares to be included in each such series, and to fix the voting powers (if any), designations, powers, preferences, and relative, participating, optional or other rights, if any, of the shares of each such series, and any qualifications, limitations or restrictions thereof. The rights, preferences and restrictions granted to and imposed on the Series A Convertible Preferred Stock, par value $0.01 per share ("Series A Preferred Stock"), and the Series B Convertible Preferred Stock, par value $0.01 per share ("Series B Preferred Stock") are set forth below in Articles VIII and IX, respectively. The rights, preferences and restrictions granted to and imposed on the Series C-1 Non-Convertible Preferred Stock, par value $0.01 per share ("C-1 Preferred"), the Series C-2 Non-Convertible Preferred Stock, par value $0.01 per share ("C-2 Preferred"), the Series C-3 Non-Convertible Preferred Stock, par value $0.01 per share ("C-3 Preferred"), and the Series C-4 Non-Convertible Preferred Stock, par value $0.01 per share ("C-4 Preferred" and, together with the C-1 Preferred, C-2 Preferred and C-3 Preferred, "Series C Preferred Stock") are set forth below in Article X.

ARTICLE VIII
SERIES A PREFERRED STOCK

SECTION 1. RANK.

The Series A Preferred Stock shall, with respect to (i) payment of dividends and distributions and (ii) rights upon any Liquidation (each of clauses (i) and (ii), an "Attribute"), rank (i) senior to all securities that are Junior Securities with respect to such Attribute, (ii) on a parity with all securities that are Parity Securities with respect to such Attribute and (iii) junior to all securities that are Senior Securities with respect to such Attribute. The Series A Preferred Stock shall rank on a parity with the Series B Preferred Stock and the Common Stock with respect to dividends and distributions and shall rank junior to the Series B Preferred Stock but senior to the Series C Preferred Stock and the Common Stock with respect to rights upon any Liquidation.

SECTION 2. DIVIDENDS AND DISTRIBUTIONS.

(a) No dividends shall be paid, and no other distribution shall be made, on or with respect to the Common Stock unless and until the holders of the Series A Preferred Stock as of the record date established by the Board of Directors for such dividend or distribution on the Common Stock shall be paid, out of funds legally available therefor, dividends in an amount (whether in the form of cash, securities or other property) equal to the amount (and in the form) of the dividends or distribution that such holder would have received had the Series A Preferred Stock been converted into Voting Common Stock immediately prior to the record date of such dividend or distribution on the Common Stock; provided, however, that if the Corporation declares and pays a dividend or makes a distribution on the Common Stock consisting in whole or in part of Common Stock or Convertible Securities, then no such dividend or distribution shall be payable in respect of the Series A Preferred Stock on account of the portion of such dividend

or distribution on the Common Stock payable in Common Stock or Convertible Securities, to the extent that an anti-dilution adjustment under Section 6(b)(i) of this Article VIII is required to be made and is made in connection with such dividend or distribution. Any such dividends or distribution shall be payable on the same payment date as the payment date for (and otherwise on the same payment terms as for) the dividends or distribution on the Common Stock established by the Board of Directors.

(b) No dividends shall be paid, and no other distribution shall be made, on or with respect to the Series B Preferred Stock (other than dividends declared and paid or distributions made by reason of a dividend or distribution with respect to the Common Stock, which shall be governed by Section 2(a) of this Article VIII, and other than dividends and distributions payable in shares of Series B Preferred Stock, which shall be governed by the proviso below) unless and until the holders of the Series A Preferred Stock as of the record date established by the Board of Directors for such dividend or distribution on the Series B Preferred Stock shall be paid, out of funds legally available therefor, dividends in respect of each share of Series A Preferred Stock in an amount (whether in the form of cash, securities or other property) equal to the amount (and in the form) of the dividends paid or distribution made with respect to a share of the Series B Preferred Stock; provided, however, that if the Corporation declares and pays a dividend or makes a distribution on the Series B Preferred Stock consisting in whole or in part of Common Stock or Convertible Securities, then no such dividend or distribution shall be payable in respect of the Series A Preferred Stock on account of the portion of such dividend or distribution on the Series B Preferred Stock payable in Common Stock or Convertible Securities, to the extent that an anti-dilution adjustment under Section 6(b)(i) of this Article VIII is required to be made and is made in connection with such dividend or distribution. Any such dividends or distribution shall be payable on the same payment date as the payment date for (and otherwise on the same payment term as for) the dividends or distribution on the Series B Preferred Stock established by the Board of Directors.

(c) If, after the Issuance Date, the Series A Preferred Stock or the Series B Preferred Stock is subdivided, combined or reclassified into a greater or lesser number of shares without a corresponding action being taken with respect to the other series of Preferred Stock, then any dividend or distribution payable with respect to the Series A Preferred Stock by reason of a dividend or distribution payable with respect to the Series B Preferred Stock shall be appropriately adjusted.

SECTION 3. REDEMPTION.

The Corporation shall have no right to redeem any shares of Series A Preferred Stock, nor shall any holder thereof have the right to require the Corporation to redeem any such shares.

SECTION 4. LIQUIDATION, DISSOLUTION OR WINDING UP.

(a) In the event the Corporation shall (i) commence a voluntary case under the federal bankruptcy laws or any other applicable federal or state bankruptcy, insolvency or similar law, (ii) consent to the entry of an order for relief in an involuntary case under any law referenced in clause (i) above or consent to the appointment of a receiver, liquidator, assignee,

custodian, trustee, or other similar official, of the Corporation or of any substantial part of its property, (iii) make a general assignment for the benefit of its creditors, (iv) admit in writing its inability to pay its debts generally as they become due, (v) have a court of competent jurisdiction enter an order or decree, which has not been withdrawn, dismissed or reversed, that is for relief against the Corporation in an involuntary case under any law referenced in clause (i) above or to appoint a receiver, liquidator, assignee, custodian, trustee, or other similar official, of the Corporation or of any substantial part of its property, and any such order or decree remains unstayed and in effect for 60 consecutive days, or (vi) otherwise liquidate, dissolve or wind up (any such event, together with any event described in the final sentence of this Section 4(a), but subject to the proviso therein, a "Liquidation"), each holder of shares of Series A Preferred Stock shall be entitled to receive out of assets of the Corporation available for distribution to its stockholders, in preference to any distribution to holders of securities that are Junior Securities with respect to a Liquidation, an amount of cash with respect to each share of Series A Preferred Stock held by such holder equal to the Liquidation Preference. For purposes of this Certificate of Incorporation, the sale, conveyance, exchange, lease, transfer or other disposition of all or substantially all of the property or assets of the Corporation or the consolidation or merger of the Corporation with or into one or more other entities (other than a wholly owned Subsidiary of the Corporation) shall be deemed to be a Liquidation; provided that any transaction in which the stockholders of the Corporation immediately prior to such transaction own shares representing more than 50% of the voting power of the outstanding shares of the surviving or acquiring corporation following the transaction (taking into account only capital stock of the Corporation held by such stockholders prior to the transaction) shall not deemed to be a Liquidation.

(b) No payment of the Liquidation Preference shall be made with respect to any share of Series A Preferred Stock unless and until the liquidation preferences payable with respect to the Series B Preferred Stock and any other securities that are Senior Securities with respect to payments upon a Liquidation shall have been paid in full. No full preferential payment on account of any Liquidation shall be made with respect to any class of securities that are Parity Securities with respect to payments upon a Liquidation unless the Liquidation Preference in respect of each share of Series A Preferred Stock shall likewise be paid at the same time in connection with such Liquidation. If, upon any Liquidation, after the distribution of the liquidation preferences to any securities that are Senior Securities with respect to payments upon a Liquidation, the assets of the Corporation are not sufficient to pay in full the Liquidation Preference payable with respect to all of the outstanding shares of Series A Preferred Stock and the full liquidation payments payable with respect to any outstanding securities that are Parity Securities with respect to payments upon a Liquidation, then such shares of Series A Preferred Stock and such Parity Securities shall share ratably in such distribution of assets in accordance with the full respective preferential payments that would be payable on such shares of Series A Preferred Stock and such Parity Securities if all amounts payable thereon were payable in full.

(c) After the payment to the holders of shares of the Series A Preferred Stock of the full amount of any liquidating distribution to which they are entitled under this Section 4, the holders of the Series A Preferred Stock as such shall have no right or claim to any of the remaining assets or the Corporation.

(d) Without limiting the voting rights of any holder of Series A Preferred Stock, the holders of shares of the Series A Preferred Stock shall be entitled to receive at least 10

Business Days prior written notice of any Liquidation, and may convert their Series A Preferred Stock at any time prior to any such Liquidation in accordance with Section 6 of this Article VIII.

SECTION 5. VOTING RIGHTS.

(a) General. Each holder of Series A Preferred Stock shall have full voting rights and powers, and shall be entitled to vote on all matters put to a vote or consent of stockholders of the Corporation, with each share of Series A Preferred Stock having the number of votes equal to the number of shares of Voting Common Stock into which such share of Series A Preferred Stock could be converted in accordance with Section 6 of this Article VIII as of the record date for the vote or consent which is being taken. The holders of the Series A Preferred Stock, the holders of the Series B Preferred Stock and the holders of Voting Common Stock (and any other class or series of capital stock entitled to vote together with the Voting Common Stock) shall vote together as a single class on all matters submitted to a vote of the stockholders of the Corporation, except as required by law or by the Certificate of Incorporation or by any certificate of designations of the Corporation from time to time in effect. Holders of Series A Preferred Stock shall be entitled to notice of all stockholders meetings in accordance with the procedures set forth in the Corporation's bylaws.

(b) Voting With Respect to Certain Matters. In addition to any matters requiring a separate vote of the Series A Preferred Stock under applicable law, the Corporation shall not, without the prior written consent or approval of the holders of more than 50% of the issued and outstanding shares of Series A Preferred Stock, voting as a single class:

(i) amend, repeal, or change the rights, preferences or privileges of the shares of Series A Preferred Stock (as in effect on the Issuance Date) in any manner that would affect adversely the shares of Series A Preferred Stock in a manner different from the effect on shares of the other classes or series of capital stock of the Corporation (including maintaining the seniority of the Series A Preferred Stock over certain other classes or series of capital stock of the Corporation, as set forth in the last sentence of Section 1 of this Article VIII as in effect on the Issuance Date); or

(ii) increase or decrease (other than by conversion of the Series A Preferred Stock into Voting Common Stock) the total number of authorized shares of Series A Preferred Stock.

(c) Number of Votes Per Share. In connection with any right to vote as a single class pursuant to Section 5(b) of this Article VIII, each holder of shares of Series A Preferred Stock shall have one vote for each share held,

SECTION 6. CONVERSION,

(a) Terms of Conversion.

(i) *Optional Conversion.* Each share of Series A Preferred Stock shall be convertible, at the option of the holder thereof, at any time, and from time to time, on the terms and conditions set forth in this Section 6, into a number of fully paid and non-assessable shares of Voting Common Stock equal to the quotient obtained by dividing (x) the Stated Value

by (y) the Conversion Price in effect on the date of such conversion. In addition, upon such conversion, the Corporation shall pay to the holder of any shares of Series A Preferred Stock being converted, out of funds legally available therefor, an amount in cash equal to any declared but unpaid dividends on the shares of Series A Preferred Stock surrendered for conversion for which the record date is a date prior to the date on which the conversion is effective pursuant to Section 6(e)(ii) of this Article VIII.

(ii) *Automatic Conversion Upon Initial Public Offering.* In the event of an automatic conversion of the Series B Preferred Stock pursuant to Section 6(a)(ii) of Article IX, then, concurrently with and effective upon such conversion of the Series B Preferred Stock, without any further action by the Corporation or the holders of shares of Series A Preferred Stock, each then outstanding share of Series A Preferred Stock shall automatically be converted into a number of fully paid and non-assessable shares of Voting Common Stock equal to the quotient obtained by dividing (x) the Stated Value by (y) the Conversion Price in effect on the date of such conversion. In addition, upon such conversion, the Corporation shall pay to each holder of any shares of Series A Preferred Stock so converted, out of funds legally available therefor, an amount in cash equal to any declared but unpaid dividends on the shares of Series A Preferred Stock so converted for which the record date is a date prior to the date on which the Initial Public Offering is consummated. The Corporation shall give each holder of Series A Preferred Stock written notice of the results of the vote referred to in Section 6(a)(ii) of Article IX within five Business Days after the date the vote is taken.

(b) Adjustment of Conversion Price. The Conversion Price shall be subject to adjustment from time to time as follows:

(i) *Stock Dividends, Splits, etc.* In case the Corporation shall, at any time or from time to time after the Issuance Date, (A) declare a dividend or make a distribution on the outstanding shares of Common Stock or Convertible Securities, in either case, in shares of Common Stock, or (B) effect a subdivision, combination or reclassification of the outstanding shares of Common Stock into a greater or lesser number of shares of Common Stock (without a comparable adjustment being made to the Series A Preferred Stock), then, and in each such case, the Conversion Price in effect immediately prior to such event or the record date therefor, whichever is earlier, shall be adjusted by multiplying such Conversion Price by a fraction of which (x) the numerator is the number of shares of Common Stock that were outstanding (as determined in accordance with Section 6(b)(vi) of this Article VIII) immediately prior to such event and (y) the denominator is the number of shares of Common Stock outstanding (as determined in accordance with Section 6(b)(vi) of this Article VIII) immediately after such event. An adjustment made pursuant to this Section 6(b)(i) shall become effective (x) in the case of any such dividend or distribution, immediately after the close of business on the date for the determination of holders of shares of Common Stock entitled to receive such dividend or distribution, or (y) in the case of any such subdivision, combination or reclassification, at the close of business on the day upon which such corporate action becomes effective.

(ii) *Issuances of Additional Shares.* In case the Corporation shall at any time or from time to time after the Issuance Date issue any Common Stock or Convertible Securities (collectively, "Additional Shares") without consideration or for a consideration per share (or having a conversion, exchange or exercise price per share) less than the Conversion

Price in effect immediately prior to such issuance, then, and in each such case, the Conversion Price in effect immediately prior to such issuance shall be reduced to an amount determined by multiplying the Conversion Price in effect immediately prior to such issuance by a fraction of which (x) the numerator is the sum of (i) the product of (A) the number of shares of Common Stock outstanding (as determined in accordance with Section 6(b)(vi) of this Article VIII) immediately prior to such issuance multiplied by (B) the Conversion Price in effect immediately prior to such issuance and (ii) the aggregate consideration received by the Corporation for the total number of shares of Common Stock so issued (or, in the case of Convertible Securities, the aggregate consideration received by the Corporation for the total amount of Convertible Securities so issued plus the aggregate consideration receivable by the Corporation for the Common Stock into or for which the Convertible Securities are convertible, exercisable or exchangeable), and (y) the denominator is the product of (i) the sum of (A) the total number of shares of Common Stock outstanding (as determined in accordance with Section 6(b)(vi) of this Article VIII) immediately prior to such issuance and (B) the number of additional shares of Common Stock so issued (or into or for which the Convertible Securities may be converted, exercised or exchanged), multiplied by (ii) the Conversion Price in effect immediately prior to such issuance. An adjustment made pursuant to this Section 6(b)(ii) shall be made on the next Business Day following the date on which any such issuance is made and shall be effective retroactively to the close of business on the date of such issuance. Notwithstanding the foregoing, no adjustment shall be made pursuant to this Section 6(b)(ii) in connection with any Excluded Issuances.

(iii) *General.* For the purposes of any adjustment of the Conversion Price pursuant to Section 6(b)(ii) of this Article VIII, the following provisions shall be applicable:

(1) In the case of the issuance of Common Stock or Convertible Securities for cash in a public offering or private placement, the aggregate consideration shall be deemed to be the amount of cash paid before deducting any discounts, commissions or placement fees payable by the Corporation to any underwriter or placement agent in connection with the issuance thereof.

(2) In the case of the issuance of Common Stock for a consideration in whole or in part other than cash, the value of the non-cash consideration received shall be the Fair Market Value of such non-cash consideration.

(3) Subparagraph (2) notwithstanding, in the case of the issuance of Additional Shares to the owners of the non-surviving entity in connection with any merger in which the Corporation is the surviving corporation, the amount of consideration therefor shall be deemed to be the Fair Market Value of such portion of the net assets and business of the non-surviving entity as is attributable to such Additional Shares.

(4) If Common Stock is sold as a unit with other securities, the aggregate consideration received for such Common Stock shall be deemed to be net of the Fair Market Value of such other securities.

(5) In the case of the issuance of Convertible Securities:

(A) The aggregate maximum number of shares of Common Stock (as set forth in the instruments relating thereto, without regard to any provision contained therein for a subsequent reduction of such number) deliverable upon conversion of or in exchange for, or upon the exercise of, such Convertible Securities and subsequent conversion, exchange or exercise thereof shall be deemed to have been issued at the time such Convertible Securities were issued and for a consideration equal to the consideration received by the Corporation for any such Convertible Securities, plus the minimum amount of consideration (as set forth in the instruments relating thereto, without regard to any provision contained therein for a subsequent increase of consideration), if any, to be received by the Corporation upon the conversion, exercise or exchange of such Convertible Securities; provided, however, that if in the case of Convertible Securities, the minimum amount of such consideration cannot be ascertained, but is a function of anti-dilution or similar protective clauses, the Corporation shall be deemed to receive the minimum amount of consideration without reference to such clause;

(B) With respect to any Convertible Securities issued after the Issuance Date for which an adjustment to the Conversion Price previously has been made pursuant to Section 6(b)(ii) of this Article VIII, upon any increase in the number of shares of Common Stock deliverable upon exercise, conversion or exchange of, or a decrease in the exercise price of, such Convertible Securities other than a change resulting from the anti-dilution provisions thereof, the applicable Conversion Price shall forthwith be readjusted retroactively to give effect to such increase or decrease;

(C) With respect to any Convertible Securities issued after the Issuance Date for which an adjustment to the Conversion Price has previously not been made pursuant to Section 6(b)(ii) of this Article VIII, if there is any increase in the number of shares of Common Stock deliverable upon exercise, conversion or exchange of, or a decrease in the exercise price of, such Convertible Securities other than a change resulting from the anti-dilution provisions thereof, such Convertible Securities shall be treated as if they had been cancelled and reissued and an adjustment to the Conversion Price with respect to such deemed issuance shall be made pursuant to Section 6(b)(ii) of this Article VIII, if applicable;

(D) With respect to any Convertible Securities issued prior to the issuance Date, if there is any increase in the number of shares of Common Stock deliverable upon exercise, conversion or exchange of, or a decrease in the exercise price of, such Convertible Securities other than a change resulting from the anti-dilution provisions thereof, such Convertible Securities shall be treated as if they had been cancelled and reissued and an adjustment to the Conversion Price with respect to such deemed issuance shall be made pursuant to Section 6(b)(ii) of this Article VIII, if applicable;

(E) No further adjustment of the Conversion Price adjusted upon the issuance of any such Convertible Securities shall be made as a result of the actual issuance of Common Stock upon the exercise, conversion or exchange of any such Convertible Securities; and

(F) On the expiration or termination of any Convertible Securities, the Conversion Price shall forthwith be recalculated to such Conversion Price as would have been calculated had the adjustment been made upon the basis of the issuance of only

the number of shares of Common Stock actually issued upon the exercise, conversion or exchange of such Convertible Securities (but taking into account other adjustments (or potential adjustments) made following the time of issuance of such Convertible Securities).

(iv) *Rights Distributions.* No adjustment of the Conversion Price pursuant to Section 6(b)(ii) of this Article VIII shall be made as the result of the adoption of a plan commonly referred to as a "Stockholders' Rights Plan" which provides for the issuance of rights to acquire shares of capital stock of the Corporation upon the occurrence of some event that is not within the control of the rights holders, or the issuance of rights under such plan; provided, however, that the issuance of capital stock of the Corporation pursuant to such rights shall require adjustment to the Conversion Price pursuant to Section 6(b)(ii) of this Article VIII.

(v) *Calculations.* All calculations of the Conversion Price shall be made to the nearest four decimal places. Anything in Section 6(b) of this Article VIII to the contrary notwithstanding, in no event shall the then current Conversion Price be increased as a result of any calculation made at any time pursuant to Section 6(b)(ii) of this Article VIII. No adjustment to the Conversion Price pursuant to Section 6(b) of this Article VIII shall be required unless such adjustment would require an increase or decrease of at least 1% in the Conversion Price; provided, however, that any adjustments which by reason of this Section 6(b)(v) are not required to be made shall be carried forward and taken into account in any subsequent adjustment.

(vi) *Outstanding Shares.* The number of shares of Common Stock at any time outstanding shall include all shares of Common Stock outstanding at such time and any shares of Common Stock issuable upon conversion or exercise of or in exchange for any Convertible Securities to the extent any such Convertible Securities are (i) convertible, exercisable or exchangeable at such time and (ii) convertible, exercisable, or exchangeable at a price that is less than the Fair Market Value of a share of Common Stock issuable upon such conversion, exercise or exchange at such time. The number of shares of Common Stock at any time outstanding shall not include any shares of Common Stock then owned or held by or for the account of the Corporation or any Subsidiary of the Corporation, and the disposition of any shares owned or held by the Corporation or any Subsidiary of the Corporation to any Person other than the Corporation or any Subsidiary of the Corporation shall be considered an issuance or sale of Common Stock.

(vii) *Successive Adjustments.* Successive adjustments in the Conversion Price shall be made, without duplication, whenever any event specified in Section 6(b)(i) or Section 6(b)(ii) of this Article VIII shall occur.

(c) Reorganization, Consolidation, Merger, Asset Sale.

(i) In case of any capital reorganization or reclassification of outstanding shares of Common Stock (other than a reclassification covered by Section 6(b) of this Article VIII), or in case of any consolidation or merger of the Corporation with or into another Person, or in case of any sale, lease, exchange, transfer, conveyance or other disposition (other than by way of merger or consolidation) of all or substantially all of the Corporation's assets, on a consolidated basis, in one transaction or a series of related transactions, to any

Person (including any group that is deemed to be a Person) (each of the foregoing being referred to as a "Series A Transaction"), in each case which is effected in such a manner that the holders of Common Stock are entitled to receive (either directly or upon subsequent liquidation) stock or other securities or property (including cash) with respect to or in exchange for Common Stock, then each share of Series A Preferred Stock then outstanding shall thereafter be convertible into, in lieu of the Voting Common Stock issuable upon such conversion prior to the consummation of such Series A Transaction, the kind and amount of shares of stock and other securities and property (including cash) receivable upon the consummation of such Series A Transaction by a holder of that number of shares of Voting Common Stock into which one share of Series A Preferred Stock was convertible immediately prior to the consummation of such Series A Transaction (including, on a pro rata basis, the cash, securities or property received by holders of Common Stock in any tender or exchange offer that is a step in such Series A Transaction); provided that if the Series A Preferred Stock becomes convertible into property, then such conversion shall be out of funds legally available therefor; and provided, however, that, in any Series A transaction where a holder effectuates a conversion pursuant to this Section 6(c), such holder shall not be entitled to receive any payment of Liquidation Preference pursuant to Section 4 of this Article VIII (it being understood that where both Section 4 of this Article VIII and this Section 6(c) are applicable to a Series A Transaction, the Corporation shall give each holder of the Series A Preferred Stock the right to elect whether to receive the Liquidation Preference pursuant to Section 4 of this Article VIII or to receive, upon conversion of the Series A Preferred Stock, the kind and amount of shares of stock and other securities and property referred to in the immediately preceding sentence). In any such case, the Corporation or the Person formed by the consolidation or resulting from the merger or which acquires such assets or which acquires the Corporation's shares, as the case may be, shall make appropriate provisions in its certificate of incorporation or other constituent document and in the definitive transaction documents relating to the Series A Transaction as to the rights and interest thereafter of the holder of shares of Series A Preferred Stock, to the end that the provisions set forth herein (including provisions with respect to changes in and other adjustments of the number of shares of Voting Common Stock issuable upon conversion of the Series A Preferred Stock and the Conversion Price) shall thereafter be applicable in relation to any shares of stock or other securities or other property deliverable upon the conversion of the shares of Series A Preferred Stock. The Corporation shall not effect any such Series A Transaction unless prior to or simultaneously with the consummation thereof the surviving corporation or purchaser, as the case may be, shall assume by written instrument the obligation to deliver to each holder of shares of Series A Preferred Stock such shares of stock, securities or other property as, in accordance with the foregoing provisions, such holder is entitled to receive, and shall have delivered such assumption agreement to such holder. In case securities or property other than Common Stock shall be issuable or deliverable upon conversion as aforesaid, then all references to Common Stock in this Section 6 shall be deemed to apply, so far as appropriate and as nearly as may be, to such other securities or property. The provisions of this Section 6(c) shall similarly apply to successive Series A Transactions. The Corporation shall give written notice to the holders of Series A Preferred Stock at least 20 Business Days prior to the date on which any Series A Transaction or similar transaction affecting the Corporation shall take place.

(ii) Nothing contained in this Section 6(c) shall limit the rights of holders of the Series A Preferred Stock to convert the Series A Preferred Stock or to vote their shares of Series A Preferred Stock in connection with a Series A Transaction.

(d) Reports. Whenever the number of shares of Voting Common Stock into which each share of Series A Preferred Stock is convertible is adjusted as provided in this Section 6, the Corporation shall promptly mail to the holders of record of the outstanding shares of Series A Preferred Stock, at their respective addresses as the same shall appear in the Corporation's transfer books, a certificate signed by an executive officer of the Corporation stating that the number of shares of Voting Common Stock into which the shares of Series A Preferred Stock are convertible has been adjusted (setting forth in reasonable detail and certifying the calculation of such adjustment), the new number of shares of Voting Common Stock (or describing the new stock, securities, cash or other property) into which each share of Series A Preferred Stock is convertible as a result of such adjustment, a brief statement of the facts requiring such adjustment and when such adjustment became effective.

(e) Conversion Procedures.

(i) The holder of any shares of Series A Preferred Stock may exercise its right to convert any or all such outstanding shares into shares of Voting Common Stock at any time by surrendering for such purpose to the Corporation, at its principal office or at such other office or agency maintained by the Corporation for that purpose, a certificate or certificates representing the shares of Series A Preferred Stock to be converted, duly endorsed in blank, accompanied by a written notice stating that such holder elects to convert all or a specified number of such shares in accordance with the provisions of this Section 6.

(ii) As promptly as practicable, and in any event within two Business Days after the surrender of such certificate or certificates and the receipt of such notice relating thereto, the Corporation shall deliver or cause to be delivered (x) certificates (which shall bear legends, if appropriate) registered in the name of such holder representing the number of shares of Voting Common Stock to which the holder of shares of Series A Preferred Stock so converted shall be entitled, (y) if less than the full number of shares of Series A Preferred Stock evidenced by the surrendered certificate or certificates are being converted, a new certificate or certificates for the number of shares evidenced by such surrendered certificate or certificates less the number of shares converted and (z) payment of all amounts to which a holder is entitled pursuant to Sections 6(a)(i) and 6(f) of this Article VIII. All shares of Voting Common Stock issuable upon conversion of the Series A Preferred Stock shall be issued without charge to the holders of Series A Preferred Stock and upon issuance shall be fully paid and non-assessable, free and clear of all taxes, liens, charges and encumbrances created, in each case, by the Corporation with respect to the issuance thereof. Such conversion shall be deemed to have been made at the close of business on the date of receipt of such notice and of such surrender of the certificate or certificates representing the shares of Series A Preferred Stock to be converted so that the rights of the holder thereof as to the shares being converted shall cease except for the right to receive shares of Voting Common Stock and any payment of amounts due pursuant to Sections 6(a)(i) and 6(f) of this Article VIII, and the Person entitled to receive the shares of Voting Common Stock shall be treated for all purposes as having become the record holder of such shares of Voting Common Stock at such time.

(iii) If a conversion of Series A Preferred Stock is to be made in connection with an Initial Public Offering (subject to the provisions of Section 6(a)(ii) of this Article VIII), a Series A Transaction or a similar transaction affecting the Corporation (other

than a tender or exchange offer), the conversion of any shares of Series A Preferred Stock may, at the election of the holder thereof, be conditioned upon the consummation of such transaction, in which case such conversion shall not be deemed to be effective until such transaction has been consummated. In connection with any tender or exchange offer for shares of Common Stock, holders of Series A Preferred Stock shall have the right to tender (or submit for exchange) shares of Series A Preferred Stock in such a manner so as to preserve the status of such shares as Series A Preferred Stock until immediately prior to such time as shares of Common Stock are to be purchased (or exchanged) pursuant to such offer, at which time that portion of the shares of Series A Preferred Stock so tendered (or submitted for exchange) which is convertible into the number of shares of Voting Common Stock to be purchased (or exchanged) pursuant to such offer shall be automatically converted into the appropriate number of shares of Voting Common Stock. Any shares of Series A Preferred Stock not so converted shall be returned to the holder as Series A Preferred Stock.

(iv) The Corporation shall not close its books against the transfer of Series A Preferred Stock or of Voting Common Stock issued or issuable upon conversion of Series A Preferred Stock in any manner which interferes with the timely conversion of Series A Preferred Stock.

(v) In the event of an automatic conversion of the Series A Preferred Stock pursuant to Section 6(a)(ii) of this Article VIII, each holder of shares of Series A Preferred Stock shall surrender for such purpose to the Corporation, at its principal office or at such other office or agency maintained by the Corporation for that purpose, the certificate or certificates representing the shares of Series A Preferred Stock held by such holder, duly endorsed in blank. As promptly as practicable after the surrender of such certificate or certificates and consummation of the Initial Public Offering, and, provided that such holder has effected such surrender at least 10 Business Days following the receipt by it of the notice referred to in Section 6(a)(ii) of this Article VIII, in sufficient time to allow such holder to participate in the Initial Public Offering, if such holder is participating, the Corporation shall deliver or cause to be delivered (x) certificates (which shall bear legends, if appropriate) registered in the name of such holder representing the number of shares of Voting Common Stock to which such holder shall be entitled, and (y) payment of all amounts to which such holder is entitled pursuant to Sections 6(a)(ii) and 6(f) of this Article VIII. All shares of Voting Common Stock issuable upon conversion of the Series A Preferred Stock shall be issued without charge to the holders of Series A Preferred Stock and upon issuance shall be fully paid and non-assessable, free and clear of all taxes, liens, charges and encumbrances created, in each case, by the Corporation with respect to the issuance thereof. Such conversion shall be deemed to have been made immediately prior to (but contingent upon) the consummation of the initial Public Offering, so that, upon the consummation of the Initial Public Offering, the rights of the holder thereof shall cease except for the right to receive shares of Voting Common Stock and any payment of amounts due pursuant to Sections 6(a)(ii) and 6(f) of this Article VIII, and the Person entitled to receive the shares of Voting Common Stock shall be treated for all purposes as having become the record holder of such shares of Voting Common Stock at such time.

(f) Fractional Shares. In connection with the conversion of any shares of Series A Preferred Stock pursuant to this Section 6, no fractions of shares of Voting Common Stock shall be issued, but in lieu thereof the Corporation shall pay a cash adjustment in respect of

such fractional interest in an amount equal to such fractional interest multiplied by the Fair Market Value of a share of Voting Common Stock on the day on which such shares of Series A Preferred Stock are deemed to have been converted. If more than one share of Series A Preferred Stock shall be surrendered for conversion at one time by the same holder, the number of full shares of Voting Common Stock issuable upon conversion thereof shall be computed on the basis of the total number of shares of Series A Preferred Stock so surrendered.

(g) Reservation of Shares. The Corporation shall at all times reserve and keep available, free from liens, charges and security interests and not subject to any preemptive rights, for issuance upon conversion of the Series A Preferred Stock, such number of its authorized but unissued shares of Voting Common Stock as will from time to time be sufficient to permit the conversion of all outstanding shares of Series A Preferred Stock, and shall take or cause to be taken all action required to increase the authorized number of shares of Voting Common Stock if necessary to permit the conversion of all outstanding shares of Series A Preferred Stock and to ensure that the shares of Voting Common Stock may be issued without violation of any applicable law or regulation or of any requirement of any securities exchange or inter-dealer quotation system on which the shares of Voting Common Stock may be listed or traded.

(h) Certain Events. If any event occurs as to which the foregoing provisions of this Section 6 are not strictly applicable or, if strictly applicable, would not, in the good faith judgment of the Board of Directors, fairly protect the conversion rights of the Series A Preferred Stock in accordance with the essential intent and principles of such provisions, then the Board of Directors shall make such adjustments in the application of such provisions, in accordance with such essential intent and principles, as shall be reasonably necessary, in the good faith opinion of the Board of Directors, to protect such conversion rights as aforesaid, but in no event shall any such adjustment have the effect of increasing the Conversion Price, or otherwise adversely affect the holders of Series A Preferred Stock,

SECTION 7. REACQUIRED SHARES.

Any shares of Series A Preferred Stock converted, purchased or otherwise acquired by the Corporation in any manner whatsoever shall have the status of authorized but unissued shares of Preferred Stock of the Corporation, without designation as to series, subject to reissuance by the Board of Directors as shares of anyone or more series.

ARTICLE IX
SERIES B PREFERRED STOCK

SECTION 1. RANK.

The Series B Preferred Stock shall, with respect to each Attribute, rank (i) senior to all securities that are Junior Securities with respect to such Attribute, (ii) on a parity with all securities that are Parity Securities with respect to such Attribute and (iii) junior to all securities that are Senior Securities with respect to such Attribute. The Series B Preferred Stock shall rank on a parity with the Series A Preferred Stock and the Common Stock with respect to dividends and distributions and shall rank senior to the Series A Preferred Stock, the Series C Preferred Stock and the Common Stock with respect to rights upon any Liquidation.

SECTION 2. DIVIDENDS AND DISTRIBUTIONS.

(a) No dividends shall be paid, and no other distribution shall be made, on or with respect to the Common Stock unless and until the holders of the Series B Preferred Stock as of the record date established by the Board of Directors for such dividend or distribution on the Common Stock shall be paid, out of funds legally available therefor, dividends in an amount (whether in the form or cash, securities or other property) equal to the amount (and in the form) of the dividends or distribution that such holder would have received had the Series B Preferred Stock been converted into Voting Common Stock immediately prior to the record date of such dividend or distribution on the Common Stock; provided, however, that if the Corporation declares and pays a dividend or makes a distribution on the Common Stock consisting in whole or in part of Common Stock or Convertible Securities, then no such dividend or distribution shall be payable in respect of the Series B Preferred Stock on account of the portion of such dividend or distribution on the Common Stock payable in Common Stock or Convertible Securities, to the extent that an anti-dilution adjustment under Section 6(b)(i) of this Article IX is required to be made and is made in connection with such dividend or distribution. Any such dividends or distribution shall be payable on the same payment date as the payment date for (and otherwise on the same payment terms as for) the dividends or distribution on the Common Stock established by the Board of Directors.

(b) No dividends shall be paid, and no other distribution shall be made, on or with respect to the Series A Preferred Stock (other than dividends declared and paid or distributions made by reason of a dividend or distribution with respect to the Common Stock, which shall be governed by Section 2(a) of this Article IX, and other than dividends and distributions payable in shares of Series A Preferred Stock, which shall be governed by the proviso below) unless and until the holders of the Series B Preferred Stock as of the record date established by the Board of Directors for such dividend or distribution on the Series A Preferred Stock shall be paid, out of funds legally available therefor, dividends in respect of each share of Series B Preferred Stock in an amount (whether in the form of cash, securities or other property) equal to the amount (and in the form) of the dividends paid or distribution made with respect to a share of the Series A Preferred Stock; provided, however, that if the Corporation declares and pays a dividend or makes a distribution on the Series A Preferred Stock consisting in whole or in part of Common Stock or Convertible Securities, then no such dividend or distribution shall be payable in respect of the Series B Preferred Stock on account of the portion of such dividend or distribution on the Series A Preferred Stock payable in Common Stock or Convertible Securities, to the extent that an anti-dilution adjustment under Section 6(b)(i) of this Article IX is required to be made and is made in connection with such dividend or distribution. Any such dividends or distribution shall be payable on the same payment date as the payment date for (and otherwise on the same payment terms as for) the dividends or distribution on the Series A Preferred Stock established by the Board of Directors.

(c) If, after the Issuance Date, the Series B Preferred Stock or the Series A Preferred Stock is subdivided, combined or reclassified into a greater or lesser number of shares without a corresponding action being taken with respect to the other series of Preferred Stock, then any dividend or distribution payable with respect to the Series B Preferred Stock by reason of a dividend or distribution payable with respect to the Series A Preferred Stock shall be appropriately adjusted.

SECTION 3. REDEMPTION.

The Corporation shall have no right to redeem any shares of Series B Preferred Stock, nor shall any holder thereof have the right to require the Corporation to redeem any such shares.

SECTION 4. LIQUIDATION, DISSOLUTION OR WINDING UP.

(a) In the event of a Liquidation, each holder of shares of the Series B Preferred Stock shall be entitled to receive out of assets of the Corporation available for distribution to its stockholders, in preference to any distribution to holders of securities that are Junior Securities with respect to a Liquidation, an amount of cash with respect to each share of Series B Preferred Stock held by such holder equal to the Liquidation Preference.

(b) No payment of the Liquidation Preference shall be made with respect to any share of Series B Preferred Stock unless and until the liquidation preferences payable with respect to any securities that are Senior Securities with respect to payments upon a Liquidation shall have been paid in full. No full preferential payment on account of any Liquidation shall be made with respect to any class of securities that are Parity Securities with respect to payments upon a Liquidation unless the Liquidation Preference in respect of each share of Series B Preferred Stock shall likewise be paid at the same time in connection with such Liquidation. If, upon any Liquidation, after the distribution of the liquidation preferences to any securities that are Senior Securities with respect to payments upon a Liquidation, the assets of the Corporation are not sufficient to pay in full the Liquidation Preference payable with respect to all of the outstanding shares of Series B Preferred Stock and the full liquidation payments payable with respect to any outstanding securities that are Parity Securities with respect to payments upon a Liquidation, then such shares of Series B Preferred Stock and such Parity Securities shall share ratably in such distribution of assets in accordance with the full respective preferential payments that would be payable on such shares of Series B Preferred Stock and such Parity Securities if all amounts payable thereon were payable in full.

(c) After the payment to the holders of shares of the Series B Preferred Stock of the full amount of any liquidating distribution to which they are entitled under this Section 4, the holders of the Series B Preferred Stock as such shall have no right or claim to any of the remaining assets of the Corporation.

(d) Without limiting the voting rights of any holder of Series B Preferred Stock, the holders of shares of the Series B Preferred Stock shall be entitled to receive at least 10 Business Days prior written notice of any Liquidation, and may convert their Series B Preferred Stock at any time prior to any such Liquidation in accordance with Section 6 of this Article IX

SECTION 5. VOTING RIGHTS.

(a) General. Each holder of Series B Preferred Stock shall have full voting rights and powers, and shall be entitled to vote on all matters put to a vote or consent of stockholders of the Corporation, with each share of Series B Preferred Stock having the number of votes equal to the number of shares of Voting Common Stock into which such share of Series B Preferred Stock could be converted in accordance with Section 6 of this Article IX as of the

record date for the vote or consent which is being taken. The holders of the Series B Preferred Stock, the holders of the Series A Preferred Stock and the holders of Voting Common Stock (and any other class or series of capital stock entitled to vote together with the Voting Common Stock) shall vote together as a single class on all matters submitted to a vote of the stockholders of the Corporation, except as required by law or by the Certificate of Incorporation or by any certificate of designations of the Corporation from time to time in effect. Holders of Series B Preferred Stock shall be entitled to notice of all stockholders meetings in accordance with the procedures set forth in the Corporation's bylaws.

(b) Voting With Respect to Certain Matters. In addition to any matters requiring a separate vote of the Series B Preferred Stock under applicable law, the Corporation shall not, without the prior written consent or approval of the holders of more than 50% of the issued and outstanding shares of Series B Preferred Stock, voting as a single class:

(i) amend, repeal, or change the rights, preferences or privileges of the shares of Series B Preferred Stock (as in effect on the Issuance Date) in any manner that would affect adversely the shares of Series B Preferred Stock in a manner different from the effect on shares of the other classes or series of capital stock of the Corporation (including maintaining the seniority of the Series B Preferred Stock over certain other classes or series of capital stock of the Corporation, as set forth in the last sentence of Section 1 of this Article IX as in effect on the Issuance Date); or

(ii) increase or decrease (other than by conversion of the Series B Preferred Stock into Voting Common Stock) the total number of authorized shares of Series B Preferred Stock.

(c) Number of Votes Per Share. In connection with any right to vote as a single class pursuant to Section 5(b) of this Article IX, each holder of shares of Series B Preferred Stock shall have one vote for each share held.

SECTION 6. CONVERSION.

(a) Terms of Conversion.

(i) *Optional Conversion.* Each share of Series B Preferred Stock shall be convertible, at the option of the holder thereof, at any time, and from time to time, on the terms and conditions set forth in this Section 6, into a number of fully paid and non-assessable shares of Voting Common Stock equal to the quotient obtained by dividing (x) the Stated Value by (y) the Conversion Price in effect on the date of such conversion. In addition, upon such conversion, the Corporation shall pay to the holder of any shares of Series B Preferred Stock being converted, out of funds legally available therefor, an amount in cash equal to any declared but unpaid dividends on the shares of Series B Preferred Stock surrendered for conversion for which the record date is a date prior to the date on which the conversion is effective pursuant to Section 6(e)(ii) of this Article IX.

(ii) *Automatic Conversion upon Initial Public Offering.* In the event there shall occur an Initial Public Offering, then, at least 30 days prior to the effective date of the registration statement relating to the Initial Public Offering, there shall be submitted to a vote of

the holders of the Series B Preferred Stock as to whether all of the outstanding shares of Series B Preferred Stock shall be converted into shares of Voting Common Stock immediately prior to the consummation of the Initial Public Offering. If the holders of at least 75% of the outstanding shares of Series B Preferred Stock vote in favor thereof, then, effective immediately prior to (but contingent upon) the consummation of the Initial Public Offering, without any further action by the Corporation or the holders of shares of Series B Preferred Stock, each then outstanding share of Series B Preferred Stock shall automatically be converted into a number of fully paid and non-assessable shares of Voting Common Stock equal to the quotient obtained by dividing (x) the Stated Value by (y) the Conversion Price in effect on the date of such conversion. In addition, upon such conversion, the Corporation shall pay to each holder of any shares of Series B Preferred Stock so converted, out of funds legally available therefor, an amount in cash equal to any declared but unpaid dividends on the shares of Series B Preferred Stock so converted for which the record date is a date prior to the date on which the Initial Public Offering is consummated. The Corporation shall give each holder of Series B Preferred Stock written notice of the results of the vote referred to in this Section 6(a)(ii) within five Business Days after the date the vote is taken.

(b) Adjustment of Conversion Price. The Conversion Price shall be subject to adjustment from time to time as follows:

(i) *Stock Dividends, Splits, etc.* In case the Corporation shall, at any time or from time to time after the Issuance Date, (A) declare a dividend or make a distribution on the outstanding shares of Common Stock or Convertible Securities, in either case, in shares of Common Stock, or (B) effect a subdivision, combination, consolidation or reclassification of the outstanding shares of Common Stock into a greater or lesser number of shares of Common Stock (without a comparable adjustment being made to the Series B Preferred Stock), then, and in each such case, the Conversion Price in effect immediately prior to such event or the record date herefor, whichever is earlier, shall be adjusted by multiplying such Conversion Price by a fraction of which (x) the numerator is the number of shares of Common Stock that were outstanding (as determined in accordance with Section 6(b)(vi) of this Article IX) immediately prior to such event and (y) the denominator is the number of shares of Common Stock outstanding (as determined in accordance with Section 6(b)(vi) of this Article IX) immediately after such event. An adjustment made pursuant to this Section 6(b)(i) shall become effective (x) in the case of any such dividend or distribution, immediately after the close of business on the date for the determination of holders of shares of Common Stock entitled to receive such dividend or distribution, or (y) in the case of any such subdivision, combination or reclassification, at the close of business on the day upon which such corporate action becomes effective.

(ii) *Issuances of Additional Shares.* In case the Corporation shall at any time or from time to time after the Issuance Date issue any Additional Shares without consideration or for a consideration per share (or having a conversion, exchange or exercise price per share) less than the Conversion Price in effect immediately prior to such issuance, then, and in each such case, the Conversion Price in effect immediately prior to such issuance shall be reduced to an amount determined by multiplying the Conversion Price in effect immediately prior to such issuance by a fraction of which (x) the numerator is the sum of (i) the product of (A) the number of shares of Common Stock outstanding (as determined in accordance with

Section 6(b)(vi) of this Article IX) immediately prior to such issuance multiplied by (B) the Conversion Price in effect immediately prior to such issuance and (ii) the aggregate consideration received by the Corporation for the total number of shares of Common Stock so issued (or, in the case of Convertible Securities, the aggregate consideration received by the Corporation for the total amount of Convertible Securities so issued plus the aggregate consideration receivable by the Corporation for the Common Stock into or for which the Convertible Securities are convertible, exercisable or exchangeable), and (y) the denominator is the product of (i) the sum of (A) the total number of shares of Common Stock outstanding (as determined in accordance with Section 6(b)(vi) of this Article IX) immediately prior to such issuance and (B) the number of additional shares of Common Stock so issued (or into or for which the Convertible Securities may be converted, exercised or exchanged), multiplied by (ii) the Conversion Price in effect immediately prior to such issuance. An adjustment made pursuant to this Section 6(b)(ii) shall be made on the next Business Day following the date on which any such issuance is made and shall be effective retroactively to the close of business on the date of such issuance. Notwithstanding the foregoing, no adjustment shall be made pursuant to this Section 6(b)(ii) in connection with any Excluded Issuances.

(iii) *General.* For the purposes of any adjustment of the Conversion Price pursuant to Section 6(b)(ii) of this Article IX, the following provisions shall be applicable:

(1) In the case of the issuance of Common Stock or Convertible Securities for cash in a public offering or private placement, the aggregate consideration shall be deemed to be the amount of cash paid before deducting any discounts, commissions or placement fees payable by the Corporation to any underwriter or placement agent in connection with the issuance thereof.

(2) In the case of the issuance of Common Stock for a consideration in whole or in part other than cash, the value of the non-cash consideration received shall be the Fair Market Value of such non-cash consideration.

(3) Subparagraph (2) notwithstanding, in the case of the issuance of Additional Shares to the owners of the non-surviving entity in connection with any merger in which the Corporation is the surviving corporation, the amount of consideration therefor shall be deemed to be the Fair Market Value of such portion of the net assets and business of the non-surviving entity as is attributable to such Additional Shares.

(4) If Common Stock is sold as a unit with other securities, the aggregate consideration received for such Common Stock shall be deemed to be net of the Fair Market Value of such other other securities.

(5) In the case of the issuance of Convertible Securities:

(A) The aggregate maximum number of shares of Common Stock (as set forth in the instruments relating thereto, without regard to any provision contained therein for a subsequent reduction of such number) deliverable upon conversion of or in exchange for, or upon the exercise of, such Convertible Securities and subsequent conversion, exchange or exercise thereof shall be deemed to have been issued at the time such Convertible

Securities were issued and for a consideration equal to the consideration received by the Corporation for any such Convertible Securities, plus the minimum amount of consideration (as set forth in the instruments relating thereto, without regard to any provision contained therein for a subsequent increase of consideration), if any, to be received by the Corporation upon the conversion, exercise or exchange of such Convertible Securities; provided, however, that if in the case of Convertible Securities, the minimum amount of such consideration cannot be ascertained, but is a function of anti-dilution or similar protective clauses, the Corporation shall be deemed to receive the minimum amount of consideration without reference to such clause;

(B) With respect to any Convertible Securities issued after the Issuance Date for which an adjustment to the Conversion Price previously has been made pursuant to Section 6(b)(ii) of this Article IX, upon any increase in the number of shares of Common Stock deliverable upon exercise, conversion or exchange of, or a decrease in the exercise price of, such Convertible Securities other than a change resulting from the anti-dilution provisions thereof, the applicable Conversion Price shall forthwith be readjusted retroactively to give effect to such increase or decrease;

(C) With respect to any Convertible Securities issued after the Issuance Date for which an adjustment to the Conversion Price has previously not been made pursuant to Section 6(b)(ii) of this Article IX, if there is any increase in the number of shares of Common Stock deliverable upon exercise, conversion or exchange of, or a decrease in the exercise price of, such Convertible Securities other than a change resulting from the anti-dilution provisions thereof, such Convertible Securities shall be treated as if they had been cancelled and reissued and an adjustment to the Conversion Price with respect to such deemed issuance shall be made pursuant to Section 6(b)(ii) of this Article IX, if applicable;

(D) With respect to any Convertible Securities issued prior to the Issuance Date, if there is any increase in the number of shares of Common Stock deliverable upon exercise, conversion or exchange of, or a decrease in the exercise price of, such Convertible Securities other than a change resulting from the anti-dilution provisions thereof, such Convertible Securities shall be treated as if they had been cancelled and reissued and an adjustment to the Conversion Price with respect to such deemed issuance shall be made pursuant to Section 6(b)(ii) of this Article IX, if applicable;

(E) No further adjustment of the Conversion Price adjusted upon the issuance of any such Convertible Securities shall be made as a result of the actual issuance of Common Stock upon the exercise, conversion or exchange of any such Convertible Securities; and

(F) On the expiration or termination of any Convertible Securities, the Conversion Price shall forthwith be recalculated to such Conversion Price as would have been calculated had the adjustment been made upon the basis of the issuance of only the number of shares or Common Stock actually issued upon the exercise, conversion or exchange of such Convertible Securities (but taking into account other adjustments (or potential adjustments) made following the time of issuance of such Convertible Securities).

(iv) *Rights Distributions.* No adjustment of the Conversion Price

pursuant to Section 6(b)(ii) of this Article IX shall be made as the result of the adoption of a plan commonly referred to as a "Stockholders' Rights Plan" which provides for the issuance of rights to acquire shares of capital stock of the Corporation upon the occurrence of some event that is not within the control of the rights holders, or the issuance of rights under such plan; provided, however, that the issuance of capital stock of the Corporation pursuant to such rights shall require adjustment to the Conversion Price pursuant to Section 6(b)(ii) of this Article IX.

(v) *Calculations.* All calculations of the Conversion Price shall be made to the nearest four decimal places. Anything in Section 6(b) of this Article IX to the contrary notwithstanding, in no event shall the then current Conversion Price be increased as a result of any calculation made at any time pursuant to Section 6(b)(ii) of this Article IX. No adjustment to the Conversion Price pursuant to Section 6(b) of this Article IX shall be required unless such adjustment would require an increase or decrease of at least 1% in the Conversion Price; provided, however, that any adjustments which by reason of this Section 6(b)(v) are not required to be made shall be carried forward and taken into account in any subsequent adjustment.

(vi) *Outstanding Shares.* The number of shares of Common Stock at any time outstanding shall include all shares of Common Stock outstanding at such time and any shares of Common Stock issuable upon conversion or exercise of or in exchange for any Convertible Securities to the extent any such Convertible Securities are (i) convertible, exercisable or exchangeable at such time and (ii) convertible, exercisable, or exchangeable at a price that is less than the Fair Market Value of a share of Common Stock issuable upon such conversion, exercise or exchange at such time. The number of shares of Common Stock at any time outstanding shall not include any shares of Common Stock then owned or held by or for the account of the Corporation or any Subsidiary of the Corporation, and the disposition of any shares owned or held by the Corporation or any Subsidiary of the Corporation to any Person other than the Corporation or any Subsidiary of the Corporation shall be considered an issuance or sale of Common Stock.

(vii) *Successive Adjustments.* Successive adjustments in the Conversion Price shall be made, without duplication, whenever any event specified in Section 6(b)(i) or Section 6(b)(ii) of this Article IX shall occur.

(c) Reorganization, Consolidation, Merger, Asset Sale.

(i) In case of any capital reorganization or reclassification of outstanding shares of Common Stock (other than a reclassification covered by Section 6(b) of this Article IX), or in case of any consolidation or merger of the Corporation with or into another Person, or in case of any sale, lease, exchange, transfer, conveyance or other disposition (other than by way of merger or consolidation) of all or substantially all of the Corporation's assets, on a consolidated basis, in one transaction or a series of related transactions, to any Person (including any group that is deemed to be a Person) (each or the foregoing being referred to as a "Series B Transaction"), in each case which is effected in such a manner that the holders of Common Stock are entitled to receive (either directly or upon subsequent liquidation) stock or other securities or property (including cash) with respect to or in exchange for Common Stock, then each share of Series B Preferred Stock then outstanding shall thereafter be convertible into,

in lieu of the Voting Common Stock issuable upon such conversion prior to the consummation of such Series B Transaction, the kind and amount of shares of stock and other securities and property (including cash) receivable upon the consummation of such Series B Transaction by a holder of that number of shares of Voting Common Stock into which one share of Series B Preferred Stock was convertible immediately prior to the consummation of such Series B Transaction (including, on a pro rata basis, the cash, securities or property received by holders of Common Stock in any tender or exchange offer that is a step in such Series B Transaction); provided that if the Series B Preferred Stock becomes convertible into property, then such conversion shall be out of funds legally available therefor; and provided, further, that, in any Series B Transaction where a holder effectuates a conversion pursuant to this Section 6(c), such holder shall not be entitled to receive any payment of Liquidation Preference pursuant to Section 4 of this Article IX (it being understood that where both Section 4 of this Article IX and this Section 6(c) are applicable to a Series B Transaction, the Corporation shall give each holder of the Series B Preferred Stock the right to elect whether to receive the Liquidation Preference pursuant to Section 4 of this Article IX or to receive, upon conversion of the Series B Preferred Stock, the kind and amount of shares of stock and other securities and property referred to in the immediately preceding sentence). In any such case, the Corporation or the Person formed by the consolidation or resulting from the merger or which acquires such assets or which acquires the Corporation's shares, as the case may be, shall make appropriate provisions in its certificate of incorporation or other constituent document and in the definitive transaction documents relating to the Series B Transaction as to the rights and interest thereafter of the holder of shares of Series B Preferred Stock, to the end that the provisions set forth herein (including provisions with respect to changes in and other adjustments of the number of shares of Voting Common Stock issuable upon conversion of the Series B Preferred Stock and the Conversion Price) shall thereafter be applicable in relation to any shares of stock or other securities or other property deliverable upon the conversion of the shares of Series B Preferred Stock. The Corporation shall not effect any such Series B Transaction unless prior to or simultaneously with the consummation thereof the surviving corporation or purchaser, as the case may be, shall assume by written instrument the obligation to deliver to each holder of shares of Series B Preferred Stock such shares of stock, securities or other property as, in accordance with the foregoing provisions, such holder is entitled to receive, and shall have delivered such assumption agreement to such holder. In case securities or property other than Common Stock shall be issuable or deliverable upon conversion as aforesaid, then all references to Common Stock in this Section 6 shall be deemed to apply, so far as appropriate and as nearly as may be, to such other securities or property. The provisions of this Section 6(c) shall similarly apply to successive Series B Transactions. The Corporation shall give written notice to the holders of Series B Preferred Stock at least 20 Business Days prior to the date on which any Series B Transaction or similar transaction affecting the Corporation shall take place.

(ii) Nothing contained in this Section 6(c) shall limit the rights of holders of the Series B Preferred Stock to convert the Series B Preferred Stock or to vote their shares of Series B Preferred Stock in connection with a Series B Transaction.

(d) Reports. Whenever the number of shares of Voting Common Stock into which each share of Series B Preferred Stock is convertible is adjusted as provided in this Section 6, the Corporation shall promptly mail to the holders of record of the outstanding shares of Series B Preferred Stock, at their respective addresses as the same shall appear in the

Corporation's transfer books, a certificate signed by an executive officer of the Corporation stating that the number of shares of Voting Common Stock into which the shares of Series B Preferred Stock are convertible has been adjusted (setting forth in reasonable detail and certifying the calculation of such adjustment), the new number of shares of Voting Common Stock (or describing the new stock, securities, cash or other property) into which each share of Series B Preferred Stock is convertible as a result of such adjustment, a brief statement of the facts requiring such adjustment and when such adjustment became effective.

(e) Conversion Procedures.

(i) The holder of any shares of Series B Preferred Stock may exercise its right to convert any or all such outstanding shares into shares of Voting Common Stock at any time by surrendering for such purpose to the Corporation, at its principal office or at such other office or agency maintained by the Corporation for that purpose, a certificate or certificates representing the shares of Series B Preferred Stock to be converted, duly endorsed in blank, accompanied by a written notice stating that such holder elects to convert all or a specified number of such shares in accordance with the provisions of this Section 6.

(ii) As promptly as practicable, and in any event within two Business Days after the surrender of such certificate or certificates and the receipt of such notice relating thereto, the Corporation shall deliver or cause to be delivered (x) certificates (which shall bear legends, if appropriate) registered in the name of such holder representing the number of shares of Voting Common Stock to which the holder of shares of Series B Preferred Stock so converted shall be entitled, (y) if less than the full number of shares of Series B Preferred Stock evidenced by the surrendered certificate or certificates are being converted, a new certificate or certificates for the number of shares evidenced by such surrendered certificate or certificates less the number of shares converted and (z) payment of all amounts to which a holder is entitled pursuant to Sections 6(a)(i) and 6(f) of this Article IX. All shares of Voting Common Stock issuable upon conversion of the Series B Preferred Stock shall be issued without charge to the holders of Series B Preferred Stock and upon issuance shall be fully paid and non-assessable, free and clear of all taxes, liens, charges and encumbrances created, in each case, by the Corporation with respect to the issuance thereof. Such conversion shall be deemed to have been made at the close of business on the date of receipt of such notice and of such surrender of the certificate or certificates representing the shares of Series B Preferred Stock to be converted so that the rights of the holder thereof as to the shares being converted shall cease except for the right to receive shares of Voting Common Stock and any payment of amounts due pursuant to Sections 6(a)(i) and 6(f) of this Article IX, and the Person entitled to receive the shares of Voting Common Stock shall be treated for all purposes as having become the record holder of such shares of Voting Common Stock at such time.

(iii) If a conversion of Series B Preferred Stock is to be made in connection with an Initial Public Offering (subject to Section 6(a)(ii) of this Article IX), a Series B Transaction or a similar transaction affecting the Corporation (other than a tender or exchange offer), the conversion of any shares of Series B Preferred Stock may, at the election of the holder thereof, be conditioned upon the consummation of such transaction, in which case such conversion shall not be deemed to be effective until such transaction has been consummated. In connection with any tender or exchange offer for shares of Common Stock, holders of Series B

Preferred Stock shall have the right to tender (or submit for exchange) shares of Series B Preferred Stock in such a manner so as to preserve the status of such shares as Series B Preferred Stock until immediately prior to such time as shares of Common Stock are to be purchased (or exchanged) pursuant to such offer, at which time that portion of the shares of Series B Preferred Stock so tendered (or submitted for exchange) which is convertible into the number of shares of Voting Common Stock to be purchased (or exchanged) pursuant to such offer shall be automatically converted into the appropriate number of shares of Voting Common Stock. Any shares of Series B Preferred Stock not so converted shall be returned to the holder as Series B Preferred Stock.

(iv) The Corporation shall not close its books against the transfer of Series B Preferred Stock or of Voting Common Stock issued or issuable upon conversion of Series B Preferred Stock in any manner which interferes with the timely conversion of Series B Preferred Stock.

(v) In the event of an automatic conversion of the Series B Preferred Stock pursuant to Section 6(a)(ii) of this Article IX, each holder of shares of Series B Preferred Stock shall surrender for such purpose to the Corporation, at its principal office or at such other office or agency maintained by the Corporation for that purpose, the certificate or certificates representing the shares of Series B Preferred Stock held by such holder, duly endorsed in blank. As promptly as practicable after the surrender of such certificate or certificates and consummation of the Initial Public Offering, and, provided that such holder has effected such surrender at least 10 Business Days following the receipt by it of the notice referred to in Section 6(a)(ii) of this Article IX, in sufficient time to allow such holder to participate in the Initial Public Offering, if such holder is participating, the Corporation shall deliver or cause to be delivered (x) certificates (which shall bear legends, if appropriate) registered in the name of such holder representing the number of shares of Voting Common Stock to which such holder shall be entitled, and (y) payment of all amounts to which such holder is entitled pursuant to Sections 6(a)(ii) and 6(f) or this Article IX. All shares of Voting Common Stock issuable upon conversion of the Series B Preferred Stock shall be issued without charge to the holders of Series B Preferred Stock and upon issuance shall be fully paid and non-assessable, free and clear of all taxes, liens, charges and encumbrances created, in each case, by the Corporation with respect to the issuance thereof. Such conversion shall be deemed to have been made immediately prior to (but contingent upon) the consummation of the Initial Public Offering, so that, upon the consummation or the Initial Public Offering, the rights of the holder thereof shall cease except for the right to receive shares of Voting Common Stock and any payment of amounts due pursuant to Sections 6(a)(ii) and 6(f) of this Article IX, and the Person entitled to receive the shares of Voting Common Stock shall be treated for all purposes as having become the record holder of such shares of Voting Common Stock at such time.

(f) Fractional Shares. In connection with the conversion of any shares of Series B Preferred Stock pursuant to this Section 6, no fractions of shares of Voting Common Stock shall be issued, but in lieu thereof the Corporation shall pay a cash adjustment in respect of such fractional interest in an amount equal to such fractional interest multiplied by the Fair Market Value of a share of Voting Common Stock on the day on which such shares of Series B Preferred Stock are deemed to have been converted. If more than one share of Series B Preferred Stock shall be surrendered for conversion at one time by the same holder, the number of full

shares of Voting Common Stock issuable upon conversion thereof shall be computed on the basis of the total number of shares of Series B Preferred Stock so surrendered.

(g) Reservation of Shares. The Corporation shall at all times reserve and keep available, free from liens, charges and security interests and not subject to any preemptive rights, for issuance upon conversion of the Series B Preferred Stock, such number of its authorized but unissued shares of Voting Common Stock as will from time to time be sufficient to permit the conversion of all outstanding shares of Series B Preferred Stock, and shall take or cause to be taken all action required to increase the authorized number of shares of Voting Common Stock if necessary to permit the conversion of all outstanding shares of Series B Preferred Stock and to ensure that the shares of Voting Common Stock may be issued without violation of any applicable law or regulation or of any requirement of any securities exchange or inter-dealer quotation system of which the shares of Voting Common Stock may be listed or traded.

(h) Certain Events. If any event occurs as to which the foregoing provisions of this Section 6 are not strictly applicable or, if strictly applicable, would not, in the good faith judgment of the Board of Directors, fairly protect the conversion rights of the Series B Preferred Stock in accordance with the essential intent and principles of such provisions, then the Board of Directors shall make such adjustments in the application of such provisions, in accordance with such essential intent and principles, as shall be reasonably necessary, in the good faith opinion of the Board of Directors, to protect such conversion rights as aforesaid, but in no event shall any such adjustment have the effect of increasing the Conversion Price, or otherwise adversely affect the holders of Series B Preferred Stock.

SECTION 7. REACQUIRED SHARES.

Any shares of Series B Preferred Stock converted, purchased or otherwise acquired by the Corporation in any manner whatsoever shall have the status of authorized but unissued shares of Preferred Stock of the Corporation, without designation as to series, subject to reissuance by the Board of Directors as shares of anyone or more series.

ARTICLE X
SERIES C PREFERRED STOCK

SECTION 1. RANK.

The Series C Preferred Stock shall rank senior to the Common Stock, but junior to the Series A Preferred Stock, the Series B Preferred Stock and all other capital stock of the Corporation, with respect to rights on Liquidation. The C-1 Preferred, the C-2 Preferred, the C-3 Preferred and the C-4 Preferred shall rank on parity with one another with respect to rights on Liquidation.

SECTION 2. DIVIDENDS.

The Series C Preferred Stock shall not be entitled to receive any dividends from the Corporation.

SECTION 3. REDEMPTION.

The Corporation shall have no right to redeem any shares of Series C Preferred Stock, nor shall any holder thereof have the right to require the Corporation to redeem any such share.

SECTION 4. LIQUIDATION, DISSOLUTION OR WINDING UP.

(a) In the event of a Liquidation, each holder of shares of C-1 Preferred, C-2 Preferred, C-3 Preferred or C-4 Preferred shall be entitled to receive out of assets of the Corporation available for distribution to its stockholders, in preference to any distribution to holders of securities that are Junior Securities with respect to a Liquidation, an amount of cash with respect to each share of C-1 Preferred, C-2 Preferred, C-3 Preferred or C-4 Preferred held by such holder equal to the Liquidation Preference.

(b) No payment of the Liquidation Preference shall be made with respect to any share of C-1 Preferred, C-2 Preferred, C-3 Preferred or C-4 Preferred unless and until the liquidation preferences payable with respect to any securities that are Senior Securities with respect to payments upon a Liquidation shall have been paid in full. No full preferential payment on account of any Liquidation shall be made with respect to any class of securities that are Parity Securities with respect to payments upon a Liquidation unless the Liquidation Preference in respect of each share of Series C Preferred Stock shall likewise be paid at the same time in connection with such Liquidation. If, upon any Liquidation, after the distribution of the liquidation preferences to any securities that are Senior Securities with respect to payments upon a Liquidation, the assets of the Corporation are not sufficient to pay in full the Liquidation Preference payable with respect to all of the outstanding shares of Series C Preferred Stock and the full liquidation payments payable with respect to any outstanding securities that are Parity Securities with respect to payments upon a Liquidation, then all such shares of Series C Preferred Stock and such Parity Securities shall share ratably in such distribution of assets in accordance with the full respective preferential payments that would be payable on such shares of Series C Preferred Stock and such Parity Securities if all amounts payable thereon were payable in full.

(c) After the payment to the holders of shares of Series C Preferred Stock of the full amount of any liquidating distribution to which they are entitled under this Section 4, the holders of Series C Preferred Stock as such shall have no right or claim to any of the remaining assets of the Corporation.

(d) Without limiting the voting rights, if any, of any holder of Series C Preferred Stock, the Corporation shall give the holders of the Series C Preferred Stock written notice at least 10 Business Days prior to the date on which the Corporation closes its books or takes a record, with respect to any Liquidation.

SECTION 5. VOTING RIGHTS.

(a) General. No holder of Series C Preferred Stock shall be entitled to any voting rights, except as hereinafter provided in this Section 5 or as required by law. Holders of Series C Preferred Stock shall be entitled to notice of all stockholders meetings to the extent provided by, and in accordance with the procedures set forth in the Corporation's bylaws.

(b) Voting Rights for Directors.

(i) The holders of C-1 Preferred, voting separately as a class, shall be entitled to elect to the Board of Directors a total of three individuals (the "C-1 Directors"), with all other stockholders of the Corporation specifically denied the right to nominate and elect the C-1 Directors.

(ii) The holders of C-2 Preferred, voting separately as a class, shall be entitled to elect to the Board of Directors one individual (the "C-2 Director"), with all other stockholders of the Corporation specifically denied the right to nominate and elect the C-2 Director.

(iii) The holders of C-3 Preferred, voting separately as a class, shall be entitled to elect to the Board of Directors one individual (the "C-3 Director"), with all other stockholders of the Corporation specifically denied the right to nominate and elect the C-3 Director.

(iv) The holders of C-4 Preferred, voting separately as a class, shall be entitled to elect to the Board of Directors one individual (the "C-4 Director"), with all other stockholders of the Corporation specifically denied the right to nominate and elect the C-4 Director.

(c) Voting With Respect to Certain Matters. In addition to any matters requiring a separate vote of the Applicable Series of the Series C Preferred Stock under applicable law, the Corporation shall not, without the prior written consent or approval of the holders of more than 50% of the issued and outstanding shares of the Applicable Series of the Series C Preferred Stock:

(i) amend, repeal, or change the rights, preferences or privileges of the shares of the Applicable Series of the Series C Preferred Stock (as in effect on the Issuance Date) in any manner that would affect adversely the shares of the Applicable Series of the Series C Preferred Stock in a manner different from the effect on shares of the other classes or series of capital stock of the Corporation (including maintaining the seniority of the Series C Preferred Stock over certain other classes or series of capital stock of the Corporation, as set forth in the first sentence of Section 1 of this Article X as in effect on the Issuance Date); or

(ii) increase or decrease the total number of authorized shares of the Applicable Series of the Series C Preferred Stock.

(d) Election Procedures.

(i) The right of the respective holders of the Applicable Series of the Series C Preferred Stock to elect directors as described in Section 5(b) of this Article X (including without limitation to fill any vacancy occurring in the office of any director elected pursuant to Section 5(b) of this Article X) may be exercised either at a special meeting of the holders of the Applicable Series of the Series C Preferred Stock, at any annual meeting of stockholders of the Corporation held for the purpose of electing directors, or by the written consent of the holders of the Applicable Series of the Series C Preferred Stock acting without a

meeting pursuant to Section 228 of the General Corporation Law of the State of Delaware. The term of office or any director elected by the holders of the Applicable Series of the Series C Preferred Stock pursuant to Section 5(b) of this Article X shall terminate upon the election of his or her successor or upon his or her earlier death, resignation or removal as provided by Section 5(d)(ii) of this Article X.

(ii) Notwithstanding anything contained in the Certificate of Incorporation or bylaws of the Corporation, any director so elected pursuant to Section 5(b) of this Article X may be removed without cause only by the holders of the Applicable Series of the Series C Preferred Stock with respect which such director was elected. The right of the holders of the Applicable Series of the Series C Preferred Stock to remove directors without cause may be exercised at any special meeting of such holders or by a written consent of such holders acting without a meeting pursuant to Section 228 of the General Corporation Law of the State of Delaware.

(iii) In case of a vacancy occurring in the office of any director so elected pursuant to Section 5(b) of this Article X, for whatever reason, the holders of the Applicable Series of the Series C Preferred Stock with respect which such director was elected may elect a successor to hold office for the unexpired term of such director or, if the vacancy is in the office of a C-1 Director, such vacancy may be filled by a majority of the other C-1 Directors (or by the sole C-1 Director) then in office.

(iv) All actions taken by the holders of the Applicable Series of the Series C Preferred Stock under this Section 5 shall be taken by the affirmative vote, or by written consent, of the holders of more than 50% of the issued and outstanding shares of the Applicable Series of the Series C Preferred Stock.

(e) Number of Votes Per Share. In connection with any right to vote as a single class pursuant to this Section 5, or on any matter required by law, each holder of shares of the Applicable Series of the Series C Preferred Stock shall have one vote for each share held.

SECTION 6. NO CONVERSION.

The shares of Series C Preferred Stock shall not be convertible into Common Stock or any other security of the Corporation.

SECTION 7. REACQUIRED SHARES.

Any shares of Series C Preferred Stock purchased or otherwise acquired by the Corporation in any manner whatsoever shall have the status of authorized but unissued shares of Preferred Stock of the Corporation, without designation as to series, subject to reissuance by the Board of Directors as shares of anyone or more series.

ARTICLE XI
BOARD OF DIRECTORS

SECTION 1. MANAGEMENT.

The business and affairs of the Corporation shall be managed by or under the direction of the Board of Directors. The Board of Directors may exercise all such authority and powers of the Corporation and do all such lawful acts and things as are not by statute or this Certificate of Incorporation directed or required to be exercised or done by the stockholders.

SECTION 2. NUMBER OF DIRECTORS.

The number of directors of the Corporation shall initially be fixed by the Board of Directors at not more than 10. The number of directors of the Corporation shall be fixed from time to time exclusively by the Board of Directors as set forth in this Section 2. The Board of Directors may, by resolution of the Board of Directors, (i) decrease the number of directors comprising the Board of Directors, but not below the number of directors then in office and not below the number that would prevent the holders of any Applicable Series of the Series C Preferred Stock from electing their Designated Director or Designated Directors, and (ii) increase the number of directors comprising the Board of Directors, in each case by the vote of a majority of the Designated Directors elected by the holders of the C-I Preferred and the vote of a majority of the other members of the Board of Directors.

SECTION 3. NEWLY-CREATED DIRECTORSHIPS AND VACANCIES.

Subject to the rights of the holders of the Series C Preferred Stock or any other series of Preferred Stock then outstanding, newly created directorships resulting from any increase in the number of directors or any vacancies in the Board of Directors resulting from death, resignation, removal from office or any other cause shall, unless otherwise required by law or resolution of the Board of Directors, be filled only by the Board of Directors by the vote of a majority of the Designated Directors elected by the holders of the C-I Preferred and the vote of a majority of the other members of the Board of Directors. A director elected to fill a newly created directorship or other vacancy shall hold office until such director's successor has been duly elected or until his or her earlier death, resignation or removal as provided in this Certificate of Incorporation.

SECTION 4. REMOVAL OF DIRECTORS.

Subject to the rights of the holders of the Series C Preferred Stock or any other series of Preferred Stock then outstanding, any director may be removed, with or without cause, from office at any time by the affirmative vote of the holders of a majority of the voting power of the issued and outstanding shares of Voting Common Stock and the issued and outstanding shares of Preferred Stock entitled to vote generally with the Voting Common Stock on all matters all which the holders of Voting Common Stock are entitled to vote, voting together as a single class; provided, however, that any Designated Director may only be removed without cause by the vote of the holders of more than 50% of the issued and outstanding shares of the Applicable Series of the Series C Preferred Stock, voting as a separate class.

SECTION 5. WRITTEN BALLOT NOT REQUIRED.

Elections of directors need not be by written ballot unless the bylaws of the

Corporation shall otherwise provide.

SECTION 6. BYLAWS.

The Board of Directors is expressly authorized to adopt, amend or repeal the bylaws or the Corporation. Any bylaws made by the directors under the powers conferred hereby may be amended or repealed by the Board of Directors or by the stockholders of the Corporation. The stockholders shall also have power to adopt, amend or repeal the bylaws of the Corporation; provided, however, that, in addition to any vote of the holders of any class or series of capital stock of the Corporation required by law, by this Certificate of Incorporation or by the bylaws, the affirmative vote of the holders of more than 50% of the voting power of the issued and outstanding shares of Voting Common Stock and the issued and outstanding shares of Preferred Stock entitled to vote generally with the Voting Common Stock on all matters on which the holders of Voting Common Stock are entitled to vote, voting together as a single class, shall be required to adopt, amend or repeal any provision of the bylaws of the Corporation.

ARTICLE XII
LIMITATION OF LIABILITY; INDEMNIFICATION

A director of the Corporation shall not be personally liable to the Corporation or its stockholders for monetary damages for breach of fiduciary duty as a director; provided, however, that the foregoing shall not eliminate or limit the liability of a director (i) for any breach of the director's duty of loyalty to the Corporation or its stockholders, (ii) for acts or omissions not in good faith or which involve intentional misconduct or a knowing violation of law, (iii) under Section 174 of the DGCL or (iv) for any transaction from which the director derived an improper personal benefit. If the DGCL is hereafter amended to permit further elimination or limitation of the personal liability of directors, then the liability of a director of the Corporation shall be eliminated or limited to the fullest extent permitted by the DGCL as so amended.

The Corporation shall, to the fullest extent permitted by applicable law, indemnify and advance expenses to each director and officer of the Corporation. The Corporation may indemnify and advance expenses to each employee and agent of the Corporation, and any other Person whom the Corporation is authorized to indemnify under the provisions of the DGCL, as provided in the bylaws or the Corporation.

Any amendment, repeal or modification of the foregoing provisions of this Article XII shall not adversely affect any right or protection of any director, officer or other agent of the Corporation existing all the time of, or increase the liability of any director, officer or other agent of the Corporation with respect to any acts or omissions of such director, officer or other agent occurring prior to, such amendment, repeal or modification.

ARTICLE XIII
AMENDMENT

The Corporation reserves the right to amend, change or repeal any provision contained in this Certificate of Incorporation, in the manner now or hereafter prescribed by statute, and all rights conferred upon stockholders herein are granted subject to this reservation.

Notwithstanding any other provision of this Certificate of Incorporation or the bylaws of the Corporation, and notwithstanding the fact that a lesser percentage or separate class vote may be specified by law, this Certificate of Incorporation, the bylaws of the Corporation or otherwise, but in addition to any affirmative vote of the holders of any particular class or series of the capital stock required by law, this Certificate of Incorporation, the bylaws of the Corporation or otherwise, the affirmative vote of the holders of more than 50% of the voting power of the issued and outstanding shares of Voting Common Stock and the issued and outstanding shares of Preferred Stock entitled to vote generally with the Voting Common Stock on all matters on which the holders of Voting Common Stock are entitled to vote, voting together as a class, shall be required to adopt any provision inconsistent with, or to amend or repeal any provision of, Articles XII or XIII of this Certificate of Incorporation.

ARTICLE XIV
NO IMPAIRMENT

The Corporation will not amend its Certificate of Incorporation or reorganize, transfer assets, consolidate, merge, dissolve, or voluntarily effect any other transaction, the sole purpose of which is to avoid the observance or performance of any of the terms to be observed or performed hereunder by the Corporation.

ARTICLE XV
PROPERTY OF STOCKHOLDERS

Except as otherwise provided by applicable law, the private property or assets of the stockholders of the Corporation shall not to any extent whatsoever be subject to the payment of the debts of the Corporation.

ARTICLE XVI
DEFINITIONS; HEADINGS

(a) For the purposes of this Certificate of Incorporation, the following definitions shall apply:

"Additional Shares" has the meaning set forth in Section 6(b)(ii) of Article VIII.

"Applicable Series of the Series C Preferred Stock" means the C-1 Preferred, the C-2 Preferred, the C-3 Preferred or the C-4 Preferred, as applicable.

"Approved Options" means (1) options to purchase up to 8,058,834 shares of Common Stock granted under the Corporation's 2007 Stock Option Plan as in effect on the Issuance Date (or as such Plan may be amended upon receipt of the Requisite Approval), which grants received the Requisite Approval, and (2) any options to purchase or other rights to acquire shares of Common Stock granted under any other equity incentive plan, the adoption of which received the Requisite Approval and which grants received the Requisite Approval.

"Arbiter" shall have the meaning ascribed to such term in the definition of "Fair Market Value."

"Attribute" has the meaning set forth in Section I of Article VIII.

"Beneficially Owned" shall mean beneficially owned as determined in accordance with Securities Exchange Act Rule 13d-3.

"Board of Directors" means the Board of Directors of the Corporation.

"Business Day" means any day other than a Saturday, Sunday, or a day on which commercial banks in the City of New York are authorized or obligated by law or executive order to close.

"Certificate of Incorporation" means the Certificate of Incorporation of the Corporation, as amended from time to time.

"Closing Price" has the meaning set forth in the definition of "Fair Market Value."

"Common Stock" means the Voting Common Stock and the Non-Voting Common Stock or either of them.

"Conversion Price" means, with respect to the Series A Preferred Stock, $1.00, subject to adjustment as provided in Section 6 of Article VIII, and, with respect to the Series B Preferred Stock, $4.6346, subject to adjustment as provided in Section 6 of Article IX.

"Convertible Securities" means (i) any options or warrants to purchase or other rights to acquire Common Stock, (ii) any securities by their terms convertible into, or exercisable or exchangeable for, Common Stock (directly or indirectly) and (iii) any options or warrants to purchase or other rights to acquire any such convertible, exercisable or exchangeable securities.

"Designated Director" means a member of the Board of Directors that was elected exclusively by the vote of one of the Applicable Series of the Series C Preferred Stock.

"Excluded Issuances" means the issuance of any shares of Common Stock or Convertible Securities (whether treasury shares or newly issued shares) (1) pursuant to a dividend or distribution on, or a subdivision, combination or reclassification of, the outstanding shares of Common Stock which, in the case of the Series A Preferred Stock, requires an adjustment in the Conversion Price pursuant to Section 6(b)(i) of Article VIII, and, in the case of the Series B Preferred Stock, requires an adjustment in the Conversion Price pursuant to Section 6(b)(i) of Article IX, (2) upon the exercise or conversion of any Convertible Securities issued on, or outstanding as of, the Issuance Date, including the Series A Preferred Stock and the Series B Preferred Stock, except, in the case of the Series A Preferred Stock, as contemplated by Section 6(b)(iii)(5)(D) of Article VIII and, in the case of the Series B Preferred Stock, as contemplated by Section 6(b)(iii)(5)(D) of Article IX, (3) pursuant to the grant or exercise of any Approved Options, (4) as consideration for the acquisition by the Corporation of another business entity or interest therein (including a joint venture or strategic alliance) by merger, stock purchase, purchase of substantially all the assets or other business combination or investment, in each case, which received the Requisite Approval, or (5) pursuant to Section 2.3 of the Preferred Stock Purchase Agreement.

"Fair Market Value" means, with respect to any security as of any date, if such security is listed or traded in a manner referred to below, an amount equal to the average of the daily Closing Prices on the twenty consecutive Trading Days immediately preceding such date. As used in this Certificate of Incorporation, the term "Closing Price", on any day, shall mean the last reported sales price on such day or, in the event no such sale takes place on such day, the average of the closing bid and asked prices, in each case on the New York Stock Exchange or, if such security is not then listed or admitted to trading on such exchange, on the principal national securities exchange on which such security is listed or admitted to trading, or, if such security is not listed or admitted to trading on any such exchange, the average of the highest reported bid and lowest reported asked prices as furnished by the National Association of Securities Dealers through the National Association of Securities Dealers Automated Quotation System ("Nasdaq") (or a similar organization if Nasdaq is no longer reporting such information). If such security is not listed and traded in a manner that the pricing information referred to above is available for the period required hereunder, or with respect to an asset other than a security (and other than cash which shall be valued at its face amount), the Fair Market Value of such security or asset shall be determined by mutual agreement between the Corporation (acting through the Board of Directors) and the holders of a majority of the outstanding shares of Series A Preferred Stock and the holders of a majority of the Series B Preferred Stock (considered as a single class, with each share of Series A Preferred Stock and each share of Series B Preferred Stock having the number or votes equal to the number of shares of Voting Common Stock into which such share of Series A Preferred Stock or Series B Preferred Stock, as applicable, may be converted) or, if the parties are unable to agree within 10 Business Days following the Corporation's written request to the holders of the Series A Preferred Stock and the holders of the Series B Preferred Stock that agreement thereon be reached, then as determined by an independent investment banking firm or valuation firm (an "Arbiter") selected by mutual agreement between the Corporation and the holders of a majority of the outstanding shares of Series A Preferred Stock and the holders of a majority of the outstanding shares of Series B Preferred Stock (determined as set forth above) (or, if the parties are unable to agree on an Arbiter within 10 Business Days of the Corporation's written request to the holders of the Series A Preferred Stock and the holders of the Series B Preferred Stock that agreement thereon be reached, then by an Arbiter selected by the New York City office of the American Arbitration Association) (with the Corporation, on the one hand, and the holders of the Series A Preferred Stock and the holders of the Series B Preferred Stock, on the other hand, each bearing one half of the fees and expenses of the Arbiter). Notwithstanding the foregoing, the determination of the Fair Market Value of a share of Voting Common Stock for purposes of Section 6(f) of Article VIII or Section 6(f) of Article IX, as applicable, shall be made by the Board of Directors, which determination shall be final and binding.

"Initial Public Offering" means the first public offering of shares of Common Stock.

"Investor Stockholders Agreement" means the Investor Stockholders Agreement, dated March 28, 2007, by and among the Corporation, the holders of the Series A Preferred Stock and the holders of the Series B Preferred Stock, as such agreement may be amended from time to time as provided in such agreement. A copy of the Investor Stockholders Agreement will be made available without charge to any stockholder upon request.

"Issuance Date" means March 28, 2007.

"Junior Securities" means:

(1) with respect to the Series A Preferred Stock, each class or series of capital stock of the Corporation now or hereafter authorized, issued or outstanding which by its terms expressly provides that it will rank junior to the Series A Preferred Stock, or which does not specify its rank, with respect to one or both of the following Attributes: (i) payment of dividends and distributions and (ii) the distribution of assets upon Liquidation;

(2) with respect to the Series B Preferred Stock, each class or series of capital stock of the Corporation now or hereafter authorized, issued or outstanding which by its terms expressly provides that it will rank junior to the Series B Preferred Stock, or which does not specify its rank, with respect to one or both of the following Attributes: (i) payment of dividends and distributions and (ii) the distribution of assets upon Liquidation; and

(3) with respect to the Series C Preferred Stock, each class or series of capital stock of the Corporation now or hereafter authorized, issued or outstanding which by its terms expressly provides that it will rank junior to the Series C Preferred Stock with respect to the distribution of assets upon Liquidation.

This definition of Junior Securities shall include any Convertible Securities exercisable or exchangeable for or convertible into any Junior Securities.

"Liquidation" has the meaning set forth in Section 4(a) of Article VIII.

"Liquidation Preference" means:

(1) with respect to a share of Series A Preferred Stock, the greater of (x) the sum of (i) the Stated Value plus (ii) an amount, if any, equal to the aggregate of any dividends declared but not yet paid on such share of Series A Preferred Stock and (y) the amount that would be payable in the Liquidation in respect of the Voting Common Stock issuable upon conversion of such share of Series A Preferred Stock if all outstanding shares of Series A Preferred Stock were converted into Voting Common Stock immediately prior to the Liquidation in accordance with Section 6 of Article VIII;

(2) with respect to a share of Series B Preferred Stock, the greater of (x) the sum of (i) the Stated Value plus (ii) an amount, if any, equal to the aggregate of any dividends declared but not yet paid on such share of Series B Preferred Stock and (y) the amount that would be payable in the Liquidation in respect of the Voting Common Stock issuable upon conversion of such share of Series B Preferred Stock if all outstanding shares of Series B Preferred Stock were converted into Voting Common Stock immediately prior to the Liquidation in accordance with Section 6 of Article IX; and

(3) with respect to a share of Series C Preferred Stock, $1.00 (as adjusted for any split, subdivision, combination, consolidation, recapitalization or similar event with respect to the Applicable Series of the Series C Preferred Stock).

"Nasdaq" has the meaning set forth in the definition of "Fair Market Value".

"Parity Securities" means:

(1) with respect to the Series A Preferred Stock, each class or series of capital stock of the Corporation now or hereafter authorized, issued or outstanding which by its terms expressly provides that it will rank on a parity with the Series A Preferred Stock with respect to one or both of the following Attributes: (i) payment of dividends and distributions and (ii) the distribution of assets upon any Liquidation;

(2) with respect to the Series B Preferred Stock, each class or series of capital stock of the Corporation now or hereafter authorized, issued or outstanding which by its terms expressly provides that it will rank on a parity with the Series B Preferred Stock with respect to one or both of the following Attributes: (i) payment of dividends and distributions and (ii) the distribution of assets upon any Liquidation; and

(3) with respect to the Series C Preferred Stock, each class or series of capital stock of the Corporation now or hereafter authorized, issued or outstanding which by its terms expressly provides that it will rank on a parity with the Series C Preferred Stock with respect to the distribution of assets upon any Liquidation.

This definition of Parity Securities shall include any Convertible Securities exercisable or exchangeable for or convertible into any Parity Securities.

"Person" means an individual, partnership, corporation, limited liability company or partnership, unincorporated organization, trust or joint venture, or a governmental agency or political subdivision thereof or other entity of any kind.

"Preferred Stock Purchase Agreement" means the Preferred Stock Purchase Agreement, dated as of February 22, 2007, by and among the Corporation, Ikaria, Inc. and purchasers of the Series B Preferred Stock, as such agreement may be amended from time to time as provided in such agreement. A copy of the Preferred Stock Purchase Agreement will be made available without charge to any stockholder upon request.

"Requisite Approval" means the approval of the Board of Directors and, if required by one or more of Sections 4.1, 4.2, 4.3, 4.4 and 4.5 of the Investor Stockholders Agreement, the approval or approvals set forth in the applicable Section or Sections of the Investor Stockholders Agreement.

"Senior Securities" means:

(1) with respect to the Series A Preferred Stock, each class or series of capital stock of the Corporation now or hereafter authorized, issued or outstanding which by its terms expressly provides that it will rank senior to the Series A Preferred Stock with respect to one or both of the following Attributes: (i) payment of dividends and distributions and (ii) the distribution of assets upon any Liquidation;

(2) with respect to the Series B Preferred Stock, each class or series of capital stock of the Corporation now or hereafter authorized, issued or outstanding which by its terms expressly provides that it will rank senior to the Series B Preferred Stock with respect to

one or both of the following Attributes: (i) payment of dividends and distributions and (ii) the distribution of assets upon any Liquidation; and

(3) with respect to the Series C Preferred Stock, each class or series of capital stock of the Corporation now or hereafter authorized, issued or outstanding which by its terms expressly provides that it will rank senior to the Series C Preferred Stock with respect to the distribution of assets upon any Liquidation.

This definition of Senior Securities shall include any Convertible Securities exercisable or exchangeable for or convertible into any Senior Securities.

"Series A Transaction" has the meaning set forth in Section 6(c)(i) of Article VIII.

"Series B Transaction" has the meaning set forth in Section 6(c)(i) of Article IX.

"Stated Value" means, with respect to a share of Series A Preferred Stock, $1.00 (as adjusted for any split, subdivision, combination, consolidation, recapitalization or similar event with respect to the Series A Preferred Stock) and, with respect to a share of Series B Preferred Stock, $4.6346 (as adjusted for any split, subdivision, combination, consolidation, recapitalization or similar event with respect to the Series B Preferred Stock).

"Subsidiary" of any Person means any corporation or other entity of which a majority of the voting power of the voting equity securities or equity interest is owned, directly or indirectly, by such Person.

"Trading Day" means a day on which the principal national securities exchange on which the Common Stock is quoted, listed or admitted to trading is open for the transaction of business.

(b) The headings of the sections, paragraphs, subparagraphs, clauses and sub-clauses included in this Certificate of Incorporation are for convenience of reference only and shall not define, limit or affect any of the provisions hereof.

IN WITNESS WHEREOF, this Restated Certificate of Incorporation, which restates and integrates and further amends the provisions of the Certificate of Incorporation of this Corporation, and which has been duly adopted in accordance with Sections 242 and 245 of the Delaware General Corporation Law, has been executed by its duly authorized officer this 7th day of May, 2010.

IKARIA HOLDINGS, INC.

/s/ Matthew M. Bennett
Name: Matthew M. Bennett
Title: Senior Vice President and Secretary

RESTATED
CERTIFICATE OF INCORPORATION
OF
IKARIA HOLDINGS, INC.
(Originally incorporated as ITL Holdings, Inc. on August 18, 2006)

ARTICLE I
NAME

The name of the Corporation is Ikaria, Inc. (the "Corporation").

ARTICLE II
REGISTERED OFFICE AND AGENT

The address of the Corporation's registered office in the State of Delaware is Corporation Service Company, 2711 Centerville Road, Suite 400, City of Wilmington 19808, County of New Castle. The name of its registered agent at such address is Corporation Service Company.

ARTICLE III
PURPOSE

The purpose of the Corporation is to engage in any lawful act or activity for which corporations may be organized under the Delaware General Corporation Law (the "DGCL").

ARTICLE IV
CAPITAL STOCK

The total number of shares of all classes of capital stock which the Corporation shall have authority to issue is two hundred thirteen million, four hundred two thousand, six hundred (213,402,600) shares, of which:

One hundred twenty five million (125,000,000) shares, par value $0.01 per share, shall be shares of common stock, of which one hundred ten million (110,000,000) shares shall be designated "Voting Common Stock" (the "Voting Common Stock") and fifteen million (15,000,000) shares shall be designated Non-Voting Common Stock" (the "Non-Voting Common Stock"); and

Eighty-eight million, four hundred two thousand, six hundred (88,402,600) shares, par value $0.01 per share, shall be shares of preferred stock (the "Preferred Stock"), of which eleven million, four hundred twenty-one thousand, three hundred (11,421,300) shares shall be designated "Series A Convertible Preferred Stock"; seventy-six million, nine hundred eighty thousand, nine hundred (76,980,900) shares shall be designated "Series B Convertible Preferred Stock"; one hundred (100) shares Shall be designated "Series C-1 Non-Convertible Preferred Stock"; one hundred (100) shares shall be designated

"Series C-2 Non-Convertible Preferred Stock"; one hundred (100) shares shall be designated "Series C-3 Non-Convertible Preferred Stock"; and one hundred (100) shares shall be designated "Series C-4 Non-Convertible Preferred Stock".

ARTICLE V
VOTING COMMON STOCK

SECTION 1. GENERAL.

Except as otherwise required by law or as expressly provided in this Certificate of Incorporation, each share of Voting Common Stock shall have the same powers, rights and privileges and shall rank equally, share ratably and be identical in all respects as to all matters, with each other share of Voting Common Stock and with each share of Non-Voting Common Stock.

SECTION 2. DIVIDENDS.

(a) Subject to the rights of the holders of Preferred Stock and to the other provisions of this Certificate of Incorporation, holders of Voting Common Stock and Non-Voting Common Stock shall be entitled to receive equally, on a per share basis, such dividends and other distributions in cash, securities or other property of the Corporation as may be declared thereon by the Board of Directors from time to time out of assets or funds of the Corporation legally available therefor.

(b) The Corporation shall not effect a subdivision, combination or reclassification of the outstanding shares of Voting Common Stock into a greater or lesser number of shares of Voting Common Stock unless a comparable adjustment is at the same time being made to the Non-Voting Common Stock.

SECTION 3. VOTING RIGHTS.

At every annual or special meeting of stockholders of the Corporation, each holder of Voting Common Stock shall be entitled to cast one vote for each share of Voting Common Stock standing in such holder's name on the stock transfer records of the Corporation; provided, however, that, except as otherwise required by law, holders of Voting Common Stock, as such, shall not be entitled to vote on any amendment to this Certificate of Incorporation (including any certificate of designation relating to any series of Preferred Stock) that relates solely to the terms of one or more outstanding series of Preferred Stock if the holders of such affected series are entitled to vote thereon, either separately or together with the holders of one or more other such series, pursuant to this Certificate of Incorporation (including pursuant to any certificate of designation relating to any series of Preferred Stock).

ARTICLE VI
NON-VOTING COMMON STOCK

SECTION 1. GENERAL.

Except as otherwise required by law or as expressly provided in this Certificate of Incorporation, each share of Non-Voting Common Stock shall have the same powers, rights and privileges and shall rank equally, share ratably and be identical in all respects as to all matters, with each other share or Non-Voting Common Stock and with each share of Voting Common Stock.

SECTION 2. DIVIDENDS.

Subject to the rights of the holders of Preferred Stock and to the other provisions of this Certificate of Incorporation, holders of Non-Voting Common Stock and Voting Common Stock shall be entitled to receive equally, on a per share basis, such dividends and other distributions in cash, securities or other property of the Corporation as may be declared thereon by the Board of Directors from time to time out of assets or funds of the Corporation legally available therefor.

SECTION 3. VOTING RIGHTS.

The holders of Non-Voting Common Stock shall not be entitled to any voting rights except as required by law.

SECTION 4. CONVERSION.

(a) In the event there shall occur an Initial Public Offering, then, immediately prior to the consummation of the Initial Public Offering, without any further action by the Corporation or the holders of shares of Non-Voting Common Stock, each outstanding share of Non-Voting Common Stock shall automatically be converted into one fully paid and non-assessable share of Voting Common Stock.

(b) The Corporation shall at all times reserve and keep available, free from liens, charges and security interests and not subject to any preemptive rights, for issuance upon conversion of the Non-Voting Common Stock, such number of its authorized but unissued shares of Voting Common Stock as will be sufficient to permit the conversion of all outstanding shares of Non-Voting Common Stock, and shall take or cause to be taken all action required to increase the authorized number of shares of Voting Common Stock if necessary to permit the conversion of all outstanding shares of Non-Voting Common Stock and to ensure that the shares of Voting Common Stock may be issued without violation of any applicable law or regulation or of any requirement of any securities exchange or inter-dealer quotation system on which the shares of Voting Common Stock may be listed or traded.

(c) The Corporation shall not effect a subdivision, combination or reclassification of the outstanding shares of Non-Voting Common Stock into a greater or lesser number of shares of Non-Voting Common Stock unless a comparable adjustment is at the same time being made to the Voting Common Stock.

ARTICLE VII
PREFERRED STOCK

The Board of Directors is authorized, subject to limitations prescribed by law, to provide by resolution or resolutions for the issuance of shares of Preferred Stock in one or more series, to establish the number of shares to be included in each such series, and to fix the voting powers (if any), designations, powers, preferences, and relative, participating, optional or other rights, if any, of the shares of each such series, and any qualifications, limitations or restrictions thereof. The rights, preferences and restrictions granted to and imposed on the Series A Convertible Preferred Stock, par value $0.01 per share ("Series A Preferred Stock"), and the Series B Convertible Preferred Stock, par value $0.01 per share ("Series B Preferred Stock") are set forth below in Articles VIII and IX, respectively. The rights, preferences and restrictions granted to and imposed on the Series C-1 Non-Convertible Preferred Stock, par value $0.01 per share ("C-1 Preferred"), the Series C-2 Non-Convertible Preferred Stock, par value $0.01 per share ("C-2 Preferred"), the Series C-3 Non-Convertible Preferred Stock, par value $0.01 per share ("C-3 Preferred"), and the Series C-4 Non-Convertible Preferred Stock, par value $0.01 per share ("C-4 Preferred" and, together with the C-1 Preferred, C-2 Preferred and C-3 Preferred, "Series C Preferred Stock") are set forth below in Article X.

ARTICLE VIII
SERIES A PREFERRED STOCK

SECTION 1. RANK.

The Series A Preferred Stock shall, with respect to (i) payment of dividends and distributions and (ii) rights upon any Liquidation (each of clauses (i) and (ii), an "Attribute"), rank (i) senior to all securities that are Junior Securities with respect to such Attribute, (ii) on a parity with all securities that are Parity Securities with respect to such Attribute and (iii) junior to all securities that are Senior Securities with respect to such Attribute. The Series A Preferred Stock shall rank on a parity with the Series B Preferred Stock and the Common Stock with respect to dividends and distributions and shall rank junior to the Series B Preferred Stock but senior to the Series C Preferred Stock and the Common Stock with respect to rights upon any Liquidation.

SECTION 2. DIVIDENDS AND DISTRIBUTIONS.

(a) No dividends shall be paid, and no other distribution shall be made, on or with respect to the Common Stock unless and until the holders of the Series A Preferred Stock as of the record date established by the Board of Directors for such dividend or distribution on the Common Stock shall be paid, out of funds legally available therefor, dividends in an amount (whether in the form of cash, securities or other property) equal to the amount (and in the form) of the dividends or distribution that such holder would have received had the Series A Preferred Stock been converted into Voting Common Stock immediately prior to the record date of such dividend or distribution on the Common Stock; provided, however, that if the Corporation declares and pays a dividend or makes a distribution on the Common Stock consisting in whole or in part of Common Stock or Convertible Securities, then no such dividend or distribution shall be payable in respect of the Series A Preferred Stock on account of the portion of such dividend

or distribution on the Common Stock payable in Common Stock or Convertible Securities, to the extent that an anti-dilution adjustment under Section 6(b)(i) of this Article VIII is required to be made and is made in connection with such dividend or distribution. Any such dividends or distribution shall be payable on the same payment date as the payment date for (and otherwise on the same payment terms as for) the dividends or distribution on the Common Stock established by the Board of Directors.

(b) No dividends shall be paid, and no other distribution shall be made, on or with respect to the Series B Preferred Stock (other than dividends declared and paid or distributions made by reason of a dividend or distribution with respect to the Common Stock, which shall be governed by Section 2(a) of this Article VIII, and other than dividends and distributions payable in shares of Series B Preferred Stock, which shall be governed by the proviso below) unless and until the holders of the Series A Preferred Stock as of the record date established by the Board of Directors for such dividend or distribution on the Series B Preferred Stock shall be paid, out of funds legally available therefor, dividends in respect of each share of Series A Preferred Stock in an amount (whether in the form of cash, securities or other property) equal to the amount (and in the form) of the dividends paid or distribution made with respect to a share of the Series B Preferred Stock; provided, however, that if the Corporation declares and pays a dividend or makes a distribution on the Series B Preferred Stock consisting in whole or in part of Common Stock or Convertible Securities, then no such dividend or distribution shall be payable in respect of the Series A Preferred Stock on account of the portion of such dividend or distribution on the Series B Preferred Stock payable in Common Stock or Convertible Securities, to the extent that an anti-dilution adjustment under Section 6(b)(i) of this Article VIII is required to be made and is made in connection with such dividend or distribution. Any such dividends or distribution shall be payable on the same payment date as the payment date for (and otherwise on the same payment term as for) the dividends or distribution on the Series B Preferred Stock established by the Board of Directors.

(c) If, after the Issuance Date, the Series A Preferred Stock or the Series B Preferred Stock is subdivided, combined or reclassified into a greater or lesser number of shares without a corresponding action being taken with respect to the other series of Preferred Stock, then any dividend or distribution payable with respect to the Series A Preferred Stock by reason of a dividend or distribution payable with respect to the Series B Preferred Stock shall be appropriately adjusted.

SECTION 3. REDEMPTION.

The Corporation shall have no right to redeem any shares of Series A Preferred Stock, nor shall any holder thereof have the right to require the Corporation to redeem any such shares.

SECTION 4. LIQUIDATION, DISSOLUTION OR WINDING UP.

(a) In the event the Corporation shall (i) commence a voluntary case under the federal bankruptcy laws or any other applicable federal or state bankruptcy, insolvency or similar law, (ii) consent to the entry of an order for relief in an involuntary case under any law referenced in clause (i) above or consent to the appointment of a receiver, liquidator, assignee,

custodian, trustee, or other similar official, of the Corporation or of any substantial part of its property, (iii) make a general assignment for the benefit of its creditors, (iv) admit in writing its inability to pay its debts generally as they become due, (v) have a court of competent jurisdiction enter an order or decree, which has not been withdrawn, dismissed or reversed, that is for relief against the Corporation in an involuntary case under any law referenced in clause (i) above or to appoint a receiver, liquidator, assignee, custodian, trustee, or other similar official, of the Corporation or of any substantial part of its property, and any such order or decree remains unstayed and in effect for 60 consecutive days, or (vi) otherwise liquidate, dissolve or wind up (any such event, together with any event described in the final sentence of this Section 4(a), but subject to the proviso therein, a "Liquidation"), each holder of shares of Series A Preferred Stock shall be entitled to receive out of assets of the Corporation available for distribution to its stockholders, in preference to any distribution to holders of securities that are Junior Securities with respect to a Liquidation, an amount of cash with respect to each share of Series A Preferred Stock held by such holder equal to the Liquidation Preference. For purposes of this Certificate of Incorporation, the sale, conveyance, exchange, lease, transfer or other disposition of all or substantially all of the property or assets of the Corporation or the consolidation or merger of the Corporation with or into one or more other entities (other than a wholly owned Subsidiary of the Corporation) shall be deemed to be a Liquidation; provided that any transaction in which the stockholders of the Corporation immediately prior to such transaction own shares representing more than 50% of the voting power of the outstanding shares of the surviving or acquiring corporation following the transaction (taking into account only capital stock of the Corporation held by such stockholders prior to the transaction) shall not deemed to be a Liquidation.

(b) No payment of the Liquidation Preference shall be made with respect to any share of Series A Preferred Stock unless and until the liquidation preferences payable with respect to the Series B Preferred Stock and any other securities that are Senior Securities with respect to payments upon a Liquidation shall have been paid in full. No full preferential payment on account of any Liquidation shall be made with respect to any class of securities that are Parity Securities with respect to payments upon a Liquidation unless the Liquidation Preference in respect of each share of Series A Preferred Stock shall likewise be paid at the same time in connection with such Liquidation. If, upon any Liquidation, after the distribution of the liquidation preferences to any securities that are Senior Securities with respect to payments upon a Liquidation, the assets of the Corporation are not sufficient to pay in full the Liquidation Preference payable with respect to all of the outstanding shares of Series A Preferred Stock and the full liquidation payments payable with respect to any outstanding securities that are Parity Securities with respect to payments upon a Liquidation, then such shares of Series A Preferred Stock and such Parity Securities shall share ratably in such distribution of assets in accordance with the full respective preferential payments that would be payable on such shares of Series A Preferred Stock and such Parity Securities if all amounts payable thereon were payable in full.

(c) After the payment to the holders of shares of the Series A Preferred Stock of the full amount of any liquidating distribution to which they are entitled under this Section 4, the holders of the Series A Preferred Stock as such shall have no right or claim to any of the remaining assets or the Corporation.

(d) Without limiting the voting rights of any holder of Series A Preferred Stock, the holders of shares of the Series A Preferred Stock shall be entitled to receive at least 10

Business Days prior written notice of any Liquidation, and may convert their Series A Preferred Stock at any time prior to any such Liquidation in accordance with Section 6 of this Article VIII.

SECTION 5. VOTING RIGHTS.

(a) General. Each holder of Series A Preferred Stock shall have full voting rights and powers, and shall be entitled to vote on all matters put to a vote or consent of stockholders of the Corporation, with each share of Series A Preferred Stock having the number of votes equal to the number of shares of Voting Common Stock into which such share of Series A Preferred Stock could be converted in accordance with Section 6 of this Article VIII as of the record date for the vote or consent which is being taken. The holders of the Series A Preferred Stock, the holders of the Series B Preferred Stock and the holders of Voting Common Stock (and any other class or series of capital stock entitled to vote together with the Voting Common Stock) shall vote together as a single class on all matters submitted to a vote of the stockholders of the Corporation, except as required by law or by the Certificate of Incorporation or by any certificate of designations of the Corporation from time to time in effect. Holders of Series A Preferred Stock shall be entitled to notice of all stockholders meetings in accordance with the procedures set forth in the Corporation's bylaws.

(b) Voting With Respect to Certain Matters. In addition to any matters requiring a separate vote of the Series A Preferred Stock under applicable law, the Corporation shall not, without the prior written consent or approval of the holders of more than 50% of the issued and outstanding shares of Series A Preferred Stock, voting as a single class:

(i) amend, repeal, or change the rights, preferences or privileges of the shares of Series A Preferred Stock (as in effect on the Issuance Date) in any manner that would affect adversely the shares of Series A Preferred Stock in a manner different from the effect on shares of the other classes or series of capital stock of the Corporation (including maintaining the seniority of the Series A Preferred Stock over certain other classes or series of capital stock of the Corporation, as set forth in the last sentence of Section 1 of this Article VIII as in effect on the Issuance Date); or

(ii) increase or decrease (other than by conversion of the Series A Preferred Stock into Voting Common Stock) the total number of authorized shares of Series A Preferred Stock.

(c) Number of Votes Per Share. In connection with any right to vote as a single class pursuant to Section 5(b) of this Article VIII, each holder of shares of Series A Preferred Stock shall have one vote for each share held,

SECTION 6. CONVERSION,

(a) Terms of Conversion.

(i) *Optional Conversion.* Each share of Series A Preferred Stock shall be convertible, at the option of the holder thereof, at any time, and from time to time, on the terms and conditions set forth in this Section 6, into a number of fully paid and non-assessable shares of Voting Common Stock equal to the quotient obtained by dividing (x) the Stated Value

by (y) the Conversion Price in effect on the date of such conversion. In addition, upon such conversion, the Corporation shall pay to the holder of any shares of Series A Preferred Stock being converted, out of funds legally available therefor, an amount in cash equal to any declared but unpaid dividends on the shares of Series A Preferred Stock surrendered for conversion for which the record date is a date prior to the date on which the conversion is effective pursuant to Section 6(e)(ii) of this Article VIII.

(ii) *Automatic Conversion Upon Initial Public Offering.* In the event of an automatic conversion of the Series B Preferred Stock pursuant to Section 6(a)(ii) of Article IX, then, concurrently with and effective upon such conversion of the Series B Preferred Stock, without any further action by the Corporation or the holders of shares of Series A Preferred Stock, each then outstanding share of Series A Preferred Stock shall automatically be converted into a number of fully paid and non-assessable shares of Voting Common Stock equal to the quotient obtained by dividing (x) the Stated Value by (y) the Conversion Price in effect on the date of such conversion. In addition, upon such conversion, the Corporation shall pay to each holder of any shares of Series A Preferred Stock so converted, out of funds legally available therefor, an amount in cash equal to any declared but unpaid dividends on the shares of Series A Preferred Stock so converted for which the record date is a date prior to the date on which the Initial Public Offering is consummated. The Corporation shall give each holder of Series A Preferred Stock written notice of the results of the vote referred to in Section 6(a)(ii) of Article IX within five Business Days after the date the vote is taken.

(b) Adjustment of Conversion Price. The Conversion Price shall be subject to adjustment from time to time as follows:

(i) *Stock Dividends, Splits, etc.* In case the Corporation shall, at any time or from time to time after the Issuance Date, (A) declare a dividend or make a distribution on the outstanding shares of Common Stock or Convertible Securities, in either case, in shares of Common Stock, or (B) effect a subdivision, combination or reclassification of the outstanding shares of Common Stock into a greater or lesser number of shares of Common Stock (without a comparable adjustment being made to the Series A Preferred Stock), then, and in each such case, the Conversion Price in effect immediately prior to such event or the record date therefor, whichever is earlier, shall be adjusted by multiplying such Conversion Price by a fraction of which (x) the numerator is the number of shares of Common Stock that were outstanding (as determined in accordance with Section 6(b)(vi) of this Article VIII) immediately prior to such event and (y) the denominator is the number of shares of Common Stock outstanding (as determined in accordance with Section 6(b)(vi) of this Article VIII) immediately after such event. An adjustment made pursuant to this Section 6(b)(i) shall become effective (x) in the case of any such dividend or distribution, immediately after the close of business on the date for the determination of holders of shares of Common Stock entitled to receive such dividend or distribution, or (y) in the case of any such subdivision, combination or reclassification, at the close of business on the day upon which such corporate action becomes effective.

(ii) *Issuances of Additional Shares.* In case the Corporation shall at any time or from time to time after the Issuance Date issue any Common Stock or Convertible Securities (collectively, "Additional Shares") without consideration or for a consideration per share (or having a conversion, exchange or exercise price per share) less than the Conversion

Price in effect immediately prior to such issuance, then, and in each such case, the Conversion Price in effect immediately prior to such issuance shall be reduced to an amount determined by multiplying the Conversion Price in effect immediately prior to such issuance by a fraction of which (x) the numerator is the sum of (i) the product of (A) the number of shares of Common Stock outstanding (as determined in accordance with Section 6(b)(vi) of this Article VIII) immediately prior to such issuance multiplied by (B) the Conversion Price in effect immediately prior to such issuance and (ii) the aggregate consideration received by the Corporation for the total number of shares of Common Stock so issued (or, in the case of Convertible Securities, the aggregate consideration received by the Corporation for the total amount of Convertible Securities so issued plus the aggregate consideration receivable by the Corporation for the Common Stock into or for which the Convertible Securities are convertible, exercisable or exchangeable), and (y) the denominator is the product of (i) the sum of (A) the total number of shares of Common Stock outstanding (as determined in accordance with Section 6(b)(vi) of this Article VIII) immediately prior to such issuance and (B) the number of additional shares of Common Stock so issued (or into or for which the Convertible Securities may be converted, exercised or exchanged), multiplied by (ii) the Conversion Price in effect immediately prior to such issuance. An adjustment made pursuant to this Section 6(b)(ii) shall be made on the next Business Day following the date on which any such issuance is made and shall be effective retroactively to the close of business on the date of such issuance. Notwithstanding the foregoing, no adjustment shall be made pursuant to this Section 6(b)(ii) in connection with any Excluded Issuances.

(iii) *General.* For the purposes of any adjustment of the Conversion Price pursuant to Section 6(b)(ii) of this Article VIII, the following provisions shall be applicable:

(1) In the case of the issuance of Common Stock or Convertible Securities for cash in a public offering or private placement, the aggregate consideration shall be deemed to be the amount of cash paid before deducting any discounts, commissions or placement fees payable by the Corporation to any underwriter or placement agent in connection with the issuance thereof.

(2) In the case of the issuance of Common Stock for a consideration in whole or in part other than cash, the value of the non-cash consideration received shall be the Fair Market Value of such non-cash consideration.

(3) Subparagraph (2) notwithstanding, in the case of the issuance of Additional Shares to the owners of the non-surviving entity in connection with any merger in which the Corporation is the surviving corporation, the amount of consideration therefor shall be deemed to be the Fair Market Value of such portion of the net assets and business of the non-surviving entity as is attributable to such Additional Shares.

(4) If Common Stock is sold as a unit with other securities, the aggregate consideration received for such Common Stock shall be deemed to be net of the Fair Market Value of such other securities.

(5) In the case of the issuance of Convertible Securities:

(A) The aggregate maximum number of shares of Common Stock (as set forth in the instruments relating thereto, without regard to any provision contained therein for a subsequent reduction of such number) deliverable upon conversion of or in exchange for, or upon the exercise of, such Convertible Securities and subsequent conversion, exchange or exercise thereof shall be deemed to have been issued at the time such Convertible Securities were issued and for a consideration equal to the consideration received by the Corporation for any such Convertible Securities, plus the minimum amount of consideration (as set forth in the instruments relating thereto, without regard to any provision contained therein for a subsequent increase of consideration), if any, to be received by the Corporation upon the conversion, exercise or exchange of such Convertible Securities; provided, however, that if in the case of Convertible Securities, the minimum amount of such consideration cannot be ascertained, but is a function of anti-dilution or similar protective clauses, the Corporation shall be deemed to receive the minimum amount of consideration without reference to such clause;

(B) With respect to any Convertible Securities issued after the Issuance Date for which an adjustment to the Conversion Price previously has been made pursuant to Section 6(b)(ii) of this Article VIII, upon any increase in the number of shares of Common Stock deliverable upon exercise, conversion or exchange of, or a decrease in the exercise price of, such Convertible Securities other than a change resulting from the anti-dilution provisions thereof, the applicable Conversion Price shall forthwith be readjusted retroactively to give effect to such increase or decrease;

(C) With respect to any Convertible Securities issued after the Issuance Date for which an adjustment to the Conversion Price has previously not been made pursuant to Section 6(b)(ii) of this Article VIII, if there is any increase in the number of shares of Common Stock deliverable upon exercise, conversion or exchange of, or a decrease in the exercise price of, such Convertible Securities other than a change resulting from the anti-dilution provisions thereof, such Convertible Securities shall be treated as if they had been cancelled and reissued and an adjustment to the Conversion Price with respect to such deemed issuance shall be made pursuant to Section 6(b)(ii) of this Article VIII, if applicable;

(D) With respect to any Convertible Securities issued prior to the issuance Date, if there is any increase in the number of shares of Common Stock deliverable upon exercise, conversion or exchange of, or a decrease in the exercise price of, such Convertible Securities other than a change resulting from the anti-dilution provisions thereof, such Convertible Securities shall be treated as if they had been cancelled and reissued and an adjustment to the Conversion Price with respect to such deemed issuance shall be made pursuant to Section 6(b)(ii) of this Article VIII, if applicable;

(E) No further adjustment of the Conversion Price adjusted upon the issuance of any such Convertible Securities shall be made as a result of the actual issuance of Common Stock upon the exercise, conversion or exchange of any such Convertible Securities; and

(F) On the expiration or termination of any Convertible Securities, the Conversion Price shall forthwith be recalculated to such Conversion Price as would have been calculated had the adjustment been made upon the basis of the issuance of only

the number of shares of Common Stock actually issued upon the exercise, conversion or exchange of such Convertible Securities (but taking into account other adjustments (or potential adjustments) made following the time of issuance of such Convertible Securities).

(iv) *Rights Distributions.* No adjustment of the Conversion Price pursuant to Section 6(b)(ii) of this Article VIII shall be made as the result of the adoption of a plan commonly referred to as a "Stockholders' Rights Plan" which provides for the issuance of rights to acquire shares of capital stock of the Corporation upon the occurrence of some event that is not within the control of the rights holders, or the issuance of rights under such plan; provided, however, that the issuance of capital stock of the Corporation pursuant to such rights shall require adjustment to the Conversion Price pursuant to Section 6(b)(ii) of this Article VIII.

(v) *Calculations.* All calculations of the Conversion Price shall be made to the nearest four decimal places. Anything in Section 6(b) of this Article VIII to the contrary notwithstanding, in no event shall the then current Conversion Price be increased as a result of any calculation made at any time pursuant to Section 6(b)(ii) of this Article VIII. No adjustment to the Conversion Price pursuant to Section 6(b) of this Article VIII shall be required unless such adjustment would require an increase or decrease of at least 1% in the Conversion Price; provided, however, that any adjustments which by reason of this Section 6(b)(v) are not required to be made shall be carried forward and taken into account in any subsequent adjustment.

(vi) *Outstanding Shares.* The number of shares of Common Stock at any time outstanding shall include all shares of Common Stock outstanding at such time and any shares of Common Stock issuable upon conversion or exercise of or in exchange for any Convertible Securities to the extent any such Convertible Securities are (i) convertible, exercisable or exchangeable at such time and (ii) convertible, exercisable, or exchangeable at a price that is less than the Fair Market Value of a share of Common Stock issuable upon such conversion, exercise or exchange at such time. The number of shares of Common Stock at any time outstanding shall not include any shares of Common Stock then owned or held by or for the account of the Corporation or any Subsidiary of the Corporation, and the disposition of any shares owned or held by the Corporation or any Subsidiary of the Corporation to any Person other than the Corporation or any Subsidiary of the Corporation shall be considered an issuance or sale of Common Stock.

(vii) *Successive Adjustments.* Successive adjustments in the Conversion Price shall be made, without duplication, whenever any event specified in Section 6(b)(i) or Section 6(b)(ii) of this Article VIII shall occur.

(c) Reorganization, Consolidation, Merger, Asset Sale.

(i) In case of any capital reorganization or reclassification of outstanding shares of Common Stock (other than a reclassification covered by Section 6(b) of this Article VIII), or in case of any consolidation or merger of the Corporation with or into another Person, or in case of any sale, lease, exchange, transfer, conveyance or other disposition (other than by way of merger or consolidation) of all or substantially all of the Corporation's assets, on a consolidated basis, in one transaction or a series of related transactions, to any

Person (including any group that is deemed to be a Person) (each of the foregoing being referred to as a "Series A Transaction"), in each case which is effected in such a manner that the holders of Common Stock are entitled to receive (either directly or upon subsequent liquidation) stock or other securities or property (including cash) with respect to or in exchange for Common Stock, then each share of Series A Preferred Stock then outstanding shall thereafter be convertible into, in lieu of the Voting Common Stock issuable upon such conversion prior to the consummation of such Series A Transaction, the kind and amount of shares of stock and other securities and property (including cash) receivable upon the consummation of such Series A Transaction by a holder of that number of shares of Voting Common Stock into which one share of Series A Preferred Stock was convertible immediately prior to the consummation of such Series A Transaction (including, on a pro rata basis, the cash, securities or property received by holders of Common Stock in any tender or exchange offer that is a step in such Series A Transaction); provided that if the Series A Preferred Stock becomes convertible into property, then such conversion shall be out of funds legally available therefor; and provided, however, that, in any Series A transaction where a holder effectuates a conversion pursuant to this Section 6(c), such holder shall not be entitled to receive any payment of Liquidation Preference pursuant to Section 4 of this Article VIII (it being understood that where both Section 4 of this Article VIII and this Section 6(c) are applicable to a Series A Transaction, the Corporation shall give each holder of the Series A Preferred Stock the right to elect whether to receive the Liquidation Preference pursuant to Section 4 of this Article VIII or to receive, upon conversion of the Series A Preferred Stock, the kind and amount of shares of stock and other securities and property referred to in the immediately preceding sentence). In any such case, the Corporation or the Person formed by the consolidation or resulting from the merger or which acquires such assets or which acquires the Corporation's shares, as the case may be, shall make appropriate provisions in its certificate of incorporation or other constituent document and in the definitive transaction documents relating to the Series A Transaction as to the rights and interest thereafter of the holder of shares of Series A Preferred Stock, to the end that the provisions set forth herein (including provisions with respect to changes in and other adjustments of the number of shares of Voting Common Stock issuable upon conversion of the Series A Preferred Stock and the Conversion Price) shall thereafter be applicable in relation to any shares of stock or other securities or other property deliverable upon the conversion of the shares of Series A Preferred Stock. The Corporation shall not effect any such Series A Transaction unless prior to or simultaneously with the consummation thereof the surviving corporation or purchaser, as the case may be, shall assume by written instrument the obligation to deliver to each holder of shares of Series A Preferred Stock such shares of stock, securities or other property as, in accordance with the foregoing provisions, such holder is entitled to receive, and shall have delivered such assumption agreement to such holder. In case securities or property other than Common Stock shall be issuable or deliverable upon conversion as aforesaid, then all references to Common Stock in this Section 6 shall be deemed to apply, so far as appropriate and as nearly as may be, to such other securities or property. The provisions of this Section 6(c) shall similarly apply to successive Series A Transactions. The Corporation shall give written notice to the holders of Series A Preferred Stock at least 20 Business Days prior to the date on which any Series A Transaction or similar transaction affecting the Corporation shall take place.

(ii) Nothing contained in this Section 6(c) shall limit the rights of holders of the Series A Preferred Stock to convert the Series A Preferred Stock or to vote their shares of Series A Preferred Stock in connection with a Series A Transaction.

(d) Reports. Whenever the number of shares of Voting Common Stock into which each share of Series A Preferred Stock is convertible is adjusted as provided in this Section 6, the Corporation shall promptly mail to the holders of record of the outstanding shares of Series A Preferred Stock, at their respective addresses as the same shall appear in the Corporation's transfer books, a certificate signed by an executive officer of the Corporation stating that the number of shares of Voting Common Stock into which the shares of Series A Preferred Stock are convertible has been adjusted (setting forth in reasonable detail and certifying the calculation of such adjustment), the new number of shares of Voting Common Stock (or describing the new stock, securities, cash or other property) into which each share of Series A Preferred Stock is convertible as a result of such adjustment, a brief statement of the facts requiring such adjustment and when such adjustment became effective.

(e) Conversion Procedures.

(i) The holder of any shares of Series A Preferred Stock may exercise its right to convert any or all such outstanding shares into shares of Voting Common Stock at any time by surrendering for such purpose to the Corporation, at its principal office or at such other office or agency maintained by the Corporation for that purpose, a certificate or certificates representing the shares of Series A Preferred Stock to be converted, duly endorsed in blank, accompanied by a written notice stating that such holder elects to convert all or a specified number of such shares in accordance with the provisions of this Section 6.

(ii) As promptly as practicable, and in any event within two Business Days after the surrender of such certificate or certificates and the receipt of such notice relating thereto, the Corporation shall deliver or cause to be delivered (x) certificates (which shall bear legends, if appropriate) registered in the name of such holder representing the number of shares of Voting Common Stock to which the holder of shares of Series A Preferred Stock so converted shall be entitled, (y) if less than the full number of shares of Series A Preferred Stock evidenced by the surrendered certificate or certificates are being converted, a new certificate or certificates for the number of shares evidenced by such surrendered certificate or certificates less the number of shares converted and (z) payment of all amounts to which a holder is entitled pursuant to Sections 6(a)(i) and 6(f) of this Article VIII. All shares of Voting Common Stock issuable upon conversion of the Series A Preferred Stock shall he issued without charge to the holders of Series A Preferred Stock and upon issuance shall be fully paid and non-assessable, free and clear of all taxes, liens, charges and encumbrances created, in each case, by the Corporation with respect to the issuance thereof. Such conversion shall be deemed to have been made at the close of business on the date of receipt of such notice and of such surrender of the certificate or certificates representing the shares of Series A Preferred Stock to be converted so that the rights of the holder thereof as to the shares being converted shall cease except for the right to receive shares of Voting Common Stock and any payment of amounts due pursuant to Sections 6(a)(i) and 6(f) of this Article VIII, and the Person entitled to receive the shares of Voting Common Stock shall be treated for all purposes as having become the record holder of such shares of Voting Common Stock at such time.

(iii) If a conversion of Series A Preferred Stock is to be made in connection with an Initial Public Offering (subject to the provisions of Section 6(a)(ii) of this Article VIII), a Series A Transaction or a similar transaction affecting the Corporation (other

than a tender or exchange offer), the conversion of any shares of Series A Preferred Stock may, at the election of the holder thereof, be conditioned upon the consummation of such transaction, in which case such conversion shall not be deemed to be effective until such transaction has been consummated. In connection with any tender or exchange offer for shares of Common Stock, holders of Series A Preferred Stock shall have the right to tender (or submit for exchange) shares of Series A Preferred Stock in such a manner so as to preserve the status of such shares as Series A Preferred Stock until immediately prior to such time as shares of Common Stock are to he purchased (or exchanged) pursuant to such offer, at which time that portion of the shares of Series A Preferred Stock so tendered (or submitted for exchange) which is convertible into the number of shares of Voting Common Stock to be purchased (or exchanged) pursuant to such offer shall be automatically converted into the appropriate number of shares of Voting Common Stock. Any shares of Series A Preferred Stock not so converted shall be returned to the holder as Series A Preferred Stock.

(iv) The Corporation shall not close its books against the transfer of Series A Preferred Stock or of Voting Common Stock issued or issuable upon conversion of Series A Preferred Stock in any manner which interferes with the timely conversion of Series A Preferred Stock.

(v) In the event of an automatic conversion of the Series A Preferred Stock pursuant to Section 6(a)(ii) of this Article VIII, each holder of shares of Series A Preferred Stock shall surrender for such purpose to the Corporation, at its principal office or at such other office or agency maintained by the Corporation for that purpose, the certificate or certificates representing the shares of Series A Preferred Stock held by such holder, duly endorsed in blank. As promptly as practicable after the surrender of such certificate or certificates and consummation of the Initial Public Offering, and, provided that such holder has effected such surrender at least 10 Business Days following the receipt by it of the notice referred to in Section 6(a)(ii) of this Article VIII, in sufficient time to allow such holder to participate in the Initial Public Offering, if such holder is participating, the Corporation shall deliver or cause to be delivered (x) certificates (which shall bear legends, if appropriate) registered in the name of such holder representing the number of shares of Voting Common Stock to which such holder shall be entitled, and (y) payment of all amounts to which such holder is entitled pursuant to Sections 6(a)(ii) and 6(f) of this Article VIII. All shares of Voting Common Stock issuable upon conversion of the Series A Preferred Stock shall be issued without charge to the holders of Series A Preferred Stock and upon issuance shall be fully paid and non-assessable, free and clear of all taxes, liens, charges and encumbrances created, in each case, by the Corporation with respect to the issuance thereof. Such conversion shall be deemed to have been made immediately prior to (but contingent upon) the consummation of the initial Public Offering, so that, upon the consummation of the Initial Public Offering, the rights of the holder thereof shall cease except for the right to receive shares of Voting Common Stock and any payment of amounts due pursuant to Sections 6(a)(ii) and 6(f) of this Article VIII, and the Person entitled to receive the shares of Voting Common Stock shall be treated for all purposes as having become the record holder of such shares of Voting Common Stock at such time.

(f) Fractional Shares. In connection with the conversion of any shares of Series A Preferred Stock pursuant to this Section 6, no fractions of shares of Voting Common Stock shall be issued, but in lieu thereof the Corporation shall pay a cash adjustment in respect of

such fractional interest in an amount equal to such fractional interest multiplied by the Fair Market Value of a share of Voting Common Stock on the day on which such shares of Series A Preferred Stock are deemed to have been converted. If more than one share of Series A Preferred Stock shall be surrendered for conversion at one time by the same holder, the number of full shares of Voting Common Stock issuable upon conversion thereof shall be computed on the basis of the total number of shares of Series A Preferred Stock so surrendered.

(g) Reservation of Shares. The Corporation shall at all times reserve and keep available, free from liens, charges and security interests and not subject to any preemptive rights, for issuance upon conversion of the Series A Preferred Stock, such number of its authorized but unissued shares of Voting Common Stock as will from time to time be sufficient to permit the conversion of all outstanding shares of Series A Preferred Stock, and shall take or cause to be taken all action required to increase the authorized number of shares of Voting Common Stock if necessary to permit the conversion of all outstanding shares of Series A Preferred Stock and to ensure that the shares of Voting Common Stock may be issued without violation of any applicable law or regulation or of any requirement of any securities exchange or inter-dealer quotation system on which the shares of Voting Common Stock may be listed or traded.

(h) Certain Events. If any event occurs as to which the foregoing provisions of this Section 6 are not strictly applicable or, if strictly applicable, would not, in the good faith judgment of the Board of Directors, fairly protect the conversion rights of the Series A Preferred Stock in accordance with the essential intent and principles of such provisions, then the Board of Directors shall make such adjustments in the application of such provisions, in accordance with such essential intent and principles, as shall be reasonably necessary, in the good faith opinion of the Board of Directors, to protect such conversion rights as aforesaid, but in no event shall any such adjustment have the effect of increasing the Conversion Price, or otherwise adversely affect the holders of Series A Preferred Stock,

SECTION 7. REACQUIRED SHARES.

Any shares of Series A Preferred Stock converted, purchased or otherwise acquired by the Corporation in any manner whatsoever shall have the status of authorized but unissued shares of Preferred Stock of the Corporation, without designation as to series, subject to reissuance by the Board of Directors as shares of anyone or more series.

ARTICLE IX
SERIES B PREFERRED STOCK

SECTION 1. RANK.

The Series B Preferred Stock shall, with respect to each Attribute, rank (i) senior to all securities that are Junior Securities with respect to such Attribute, (ii) on a parity with all securities that are Parity Securities with respect to such Attribute and (iii) junior to all securities that are Senior Securities with respect to such Attribute. The Series B Preferred Stock shall rank on a parity with the Series A Preferred Stock and the Common Stock with respect to dividends and distributions and shall rank senior to the Series A Preferred Stock, the Series C Preferred Stock and the Common Stock with respect to rights upon any Liquidation.

SECTION 2. DIVIDENDS AND DISTRIBUTIONS.

(a) No dividends shall be paid, and no other distribution shall be made, on or with respect to the Common Stock unless and until the holders of the Series B Preferred Stock as of the record date established by the Board of Directors for such dividend or distribution on the Common Stock shall be paid, out of funds legally available therefor, dividends in an amount (whether in the form or cash, securities or other property) equal to the amount (and in the form) of the dividends or distribution that such holder would have received had the Series B Preferred Stock been converted into Voting Common Stock immediately prior to the record date of such dividend or distribution on the Common Stock; provided, however, that if the Corporation declares and pays a dividend or makes a distribution on the Common Stock consisting in whole or in part of Common Stock or Convertible Securities, then no such dividend or distribution shall be payable in respect of the Series B Preferred Stock on account of the portion of such dividend or distribution on the Common Stock payable in Common Stock or Convertible Securities, to the extent that an anti-dilution adjustment under Section 6(b)(i) of this Article IX is required to be made and is made in connection with such dividend or distribution. Any such dividends or distribution shall be payable on the same payment date as the payment date for (and otherwise on the same payment terms as for) the dividends or distribution on the Common Stock established by the Board of Directors.

(b) No dividends shall be paid, and no other distribution shall be made, on or with respect to the Series A Preferred Stock (other than dividends declared and paid or distributions made by reason of a dividend or distribution with respect to the Common Stock, which shall be governed by Section 2(a) of this Article IX, and other than dividends and distributions payable in shares of Series A Preferred Stock, which shall be governed by the proviso below) unless and until the holders of the Series B Preferred Stock as of the record date established by the Board of Directors for such dividend or distribution on the Series A Preferred Stock shall be paid, out of funds legally available therefor, dividends in respect of each share of Series B Preferred Stock in an amount (whether in the form of cash, securities or other property) equal to the amount (and in the form) of the dividends paid or distribution made with respect to a share of the Series A Preferred Stock; provided, however, that if the Corporation declares and pays a dividend or makes a distribution on the Series A Preferred Stock consisting in whole or in part of Common Stock or Convertible Securities, then no such dividend or distribution shall be payable in respect of the Series B Preferred Stock on account of the portion of such dividend or distribution on the Series A Preferred Stock payable in Common Stock or Convertible Securities, to the extent that an anti-dilution adjustment under Section 6(b)(i) of this Article IX is required to be made and is made in connection with such dividend or distribution. Any such dividends or distribution shall be payable on the same payment date as the payment date for (and otherwise on the same payment terms as for) the dividends or distribution on the Series A Preferred Stock established by the Board of Directors.

(c) If, after the Issuance Date, the Series B Preferred Stock or the Series A Preferred Stock is subdivided, combined or reclassified into a greater or lesser number of shares without a corresponding action being taken with respect to the other series of Preferred Stock, then any dividend or distribution payable with respect to the Series B Preferred Stock by reason of a dividend or distribution payable with respect to the Series A Preferred Stock shall be appropriately adjusted.

SECTION 3. REDEMPTION.

The Corporation shall have no right to redeem any shares of Series B Preferred Stock, nor shall any holder thereof have the right to require the Corporation to redeem any such shares.

SECTION 4. LIQUIDATION, DISSOLUTION OR WINDING UP.

(a) In the event of a Liquidation, each holder of shares of the Series B Preferred Stock shall be entitled to receive out of assets of the Corporation available for distribution to its stockholders, in preference to any distribution to holders of securities that are Junior Securities with respect to a Liquidation, an amount of cash with respect to each share of Series B Preferred Stock held by such holder equal to the Liquidation Preference.

(b) No payment of the Liquidation Preference shall be made with respect to any share of Series B Preferred Stock unless and until the liquidation preferences payable with respect to any securities that are Senior Securities with respect to payments upon a Liquidation shall have been paid in full. No full preferential payment on account of any Liquidation shall be made with respect to any class of securities that are Parity Securities with respect to payments upon a Liquidation unless the Liquidation Preference in respect of each share of Series B Preferred Stock shall likewise be paid at the same time in connection with such Liquidation. If, upon any Liquidation, after the distribution of the liquidation preferences to any securities that are Senior Securities with respect to payments upon a Liquidation, the assets of the Corporation are not sufficient to pay in full the Liquidation Preference payable with respect to all of the outstanding shares of Series B Preferred Stock and the full liquidation payments payable with respect to any outstanding securities that are Parity Securities with respect to payments upon a Liquidation, then such shares of Series B Preferred Stock and such Parity Securities shall share ratably in such distribution of assets in accordance with the full respective preferential payments that would be payable on such shares of Series B Preferred Stock and such Parity Securities if all amounts payable thereon were payable in full.

(c) After the payment to the holders of shares of the Series B Preferred Stock of the full amount of any liquidating distribution to which they are entitled under this Section 4, the holders of the Series B Preferred Stock as such shall have no right or claim to any of the remaining assets of the Corporation.

(d) Without limiting the voting rights of any holder of Series B Preferred Stock, the holders of shares of the Series B Preferred Stock shall be entitled to receive at least 10 Business Days prior written notice of any Liquidation, and may convert their Series B Preferred Stock at any time prior to any such Liquidation in accordance with Section 6 of this Article IX

SECTION 5. VOTING RIGHTS.

(a) General. Each holder of Series B Preferred Stock shall have full voting rights and powers, and shall be entitled to vote on all matters put to a vote or consent of stockholders of the Corporation, with each share of Series B Preferred Stock having the number of votes equal to the number of shares of Voting Common Stock into which such share of Series B Preferred Stock could be converted in accordance with Section 6 of this Article IX as of the

record date for the vote or consent which is being taken. The holders of the Series B Preferred Stock, the holders of the Series A Preferred Stock and the holders of Voting Common Stock (and any other class or series of capital stock entitled to vote together with the Voting Common Stock) shall vote together as a single class on all matters submitted to a vote of the stockholders of the Corporation, except as required by law or by the Certificate of Incorporation or by any certificate of designations of the Corporation from time to time in effect. Holders of Series B Preferred Stock shall be entitled to notice of all stockholders meetings in accordance with the procedures set forth in the Corporation's bylaws.

(b) Voting With Respect to Certain Matters. In addition to any matters requiring a separate vote of the Series B Preferred Stock under applicable law, the Corporation shall not, without the prior written consent or approval of the holders of more than 50% of the issued and outstanding shares of Series B Preferred Stock, voting as a single class:

(i) amend, repeal, or change the rights, preferences or privileges of the shares of Series B Preferred Stock (as in effect on the Issuance Date) in any manner that would affect adversely the shares of Series B Preferred Stock in a manner different from the effect on shares of the other classes or series of capital stock of the Corporation (including maintaining the seniority of the Series B Preferred Stock over certain other classes or series of capital stock of the Corporation, as set forth in the last sentence of Section 1 of this Article IX as in effect on the Issuance Date); or

(ii) increase or decrease (other than by conversion of the Series B Preferred Stock into Voting Common Stock) the total number of authorized shares of Series B Preferred Stock.

(c) Number of Votes Per Share. In connection with any right to vote as a single class pursuant to Section 5(b) of this Article IX, each holder of shares of Series B Preferred Stock shall have one vote for each share held.

SECTION 6. CONVERSION.

(a) Terms of Conversion.

(i) *Optional Conversion.* Each share of Series B Preferred Stock shall be convertible, at the option of the holder thereof, at any time, and from time to time, on the terms and conditions set forth in this Section 6, into a number of fully paid and non-assessable shares of Voting Common Stock equal to the quotient obtained by dividing (x) the Stated Value by (y) the Conversion Price in effect on the date of such conversion. In addition, upon such conversion, the Corporation shall pay to the holder of any shares of Series B Preferred Stock being converted, out of funds legally available therefor, an amount in cash equal to any declared but unpaid dividends on the shares of Series B Preferred Stock surrendered for conversion for which the record date is a date prior to the date on which the conversion is effective pursuant to Section 6(e)(ii) of this Article IX.

(ii) *Automatic Conversion upon Initial Public Offering.* In the event there shall occur an Initial Public Offering, then, at least 30 days prior to the effective date of the registration statement relating to the Initial Public Offering, there shall be submitted to a vote of

the holders of the Series B Preferred Stock as to whether all of the outstanding shares of Series B Preferred Stock shall be converted into shares of Voting Common Stock immediately prior to the consummation of the Initial Public Offering. If the holders of at least 75% of the outstanding shares of Series B Preferred Stock vote in favor thereof, then, effective immediately prior to (but contingent upon) the consummation of the Initial Public Offering, without any further action by the Corporation or the holders of shares of Series B Preferred Stock, each then outstanding share of Series B Preferred Stock shall automatically be converted into a number of fully paid and non-assessable shares of Voting Common Stock equal to the quotient obtained by dividing (x) the Stated Value by (y) the Conversion Price in effect on the date of such conversion. In addition, upon such conversion, the Corporation shall pay to each holder of any shares of Series B Preferred Stock so converted, out of funds legally available therefor, an amount in cash equal to any declared but unpaid dividends on the shares of Series B Preferred Stock so converted for which the record date is a date prior to the date on which the Initial Public Offering is consummated. The Corporation shall give each holder of Series B Preferred Stock written notice of the results of the vote referred to in this Section 6(a)(ii) within five Business Days after the date the vote is taken.

(b) Adjustment of Conversion Price. The Conversion Price shall be subject to adjustment from time to time as follows:

(i) *Stock Dividends, Splits, etc.* In case the Corporation shall, at any time or from time to time after the Issuance Date, (A) declare a dividend or make a distribution on the outstanding shares of Common Stock or Convertible Securities, in either case, in shares of Common Stock, or (B) effect a subdivision, combination, consolidation or reclassification of the outstanding shares of Common Stock into a greater or lesser number of shares of Common Stock (without a comparable adjustment being made to the Series B Preferred Stock), then, and in each such case, the Conversion Price in effect immediately prior to such event or the record date herefor, whichever is earlier, shall be adjusted by multiplying such Conversion Price by a fraction of which (x) the numerator is the number of shares of Common Stock that were outstanding (as determined in accordance with Section 6(b)(vi) of this Article IX) immediately prior to such event and (y) the denominator is the number of shares of Common Stock outstanding (as determined in accordance with Section 6(b)(vi) of this Article IX) immediately after such event. An adjustment made pursuant to this Section 6(b)(i) shall become effective (x) in the case of any such dividend or distribution, immediately after the close of business on the date for the determination of holders of shares of Common Stock entitled to receive such dividend or distribution, or (y) in the case of any such subdivision, combination or reclassification, at the close of business on the day upon which such corporate action becomes effective.

(ii) *Issuances of Additional Shares.* In case the Corporation shall at any time or from time to time after the Issuance Date issue any Additional Shares without consideration or for a consideration per share (or having a conversion, exchange or exercise price per share) less than the Conversion Price in effect immediately prior to such issuance, then, and in each such case, the Conversion Price in effect immediately prior to such issuance shall be reduced to an amount determined by multiplying the Conversion Price in effect immediately prior to such issuance by a fraction of which (x) the numerator is the sum of (i) the product of (A) the number of shares of Common Stock outstanding (as determined in accordance with

Section 6(b)(vi) of this Article IX) immediately prior to such issuance multiplied by (B) the Conversion Price in effect immediately prior to such issuance and (ii) the aggregate consideration received by the Corporation for the total number of shares of Common Stock so issued (or, in the case of Convertible Securities, the aggregate consideration received by the Corporation for the total amount of Convertible Securities so issued plus the aggregate consideration receivable by the Corporation for the Common Stock into or for which the Convertible Securities are convertible, exercisable or exchangeable), and (y) the denominator is the product of (i) the sum of (A) the total number of shares of Common Stock outstanding (as determined in accordance with Section 6(b)(vi) of this Article IX) immediately prior to such issuance and (B) the number of additional shares of Common Stock so issued (or into or for which the Convertible Securities may be converted, exercised or exchanged), multiplied by (ii) the Conversion Price in effect immediately prior to such issuance. An adjustment made pursuant to this Section 6(b)(ii) shall be made on the next Business Day following the date on which any such issuance is made and shall be effective retroactively to the close of business on the date of such issuance. Notwithstanding the foregoing, no adjustment shall be made pursuant to this Section 6(b)(ii) in connection with any Excluded Issuances.

(iii) *General.* For the purposes of any adjustment of the Conversion Price pursuant to Section 6(b)(ii) of this Article IX, the following provisions shall be applicable:

(1) In the case of the issuance of Common Stock or Convertible Securities for cash in a public offering or private placement, the aggregate consideration shall be deemed to be the amount of cash paid before deducting any discounts, commissions or placement fees payable by the Corporation to any underwriter or placement agent in connection with the issuance thereof.

(2) In the case of the issuance of Common Stock for a consideration in whole or in part other than cash, the value of the non-cash consideration received shall be the Fair Market Value of such non-cash consideration.

(3) Subparagraph (2) notwithstanding, in the case of the issuance of Additional Shares to the owners of the non-surviving entity in connection with any merger in which the Corporation is the surviving corporation, the amount of consideration therefor shall be deemed to be the Fair Market Value of such portion of the net assets and business of the non-surviving entity as is attributable to such Additional Shares.

(4) If Common Stock is sold as a unit with other securities, the aggregate consideration received for such Common Stock shall be deemed to be net of the Fair Market Value of such other other securities.

(5) In the case of the issuance of Convertible Securities:

(A) The aggregate maximum number of shares of Common Stock (as set forth in the instruments relating thereto, without regard to any provision contained therein for a subsequent reduction of such number) deliverable upon conversion of or in exchange for, or upon the exercise of, such Convertible Securities and subsequent conversion, exchange or exercise thereof shall be deemed to have been issued at the time such Convertible

Securities were issued and for a consideration equal to the consideration received by the Corporation for any such Convertible Securities, plus the minimum amount of consideration (as set forth in the instruments relating thereto, without regard to any provision contained therein for a subsequent increase of consideration), if any, to be received by the Corporation upon the conversion, exercise or exchange of such Convertible Securities; provided, however, that if in the case of Convertible Securities, the minimum amount of such consideration cannot be ascertained, but is a function of anti-dilution or similar protective clauses, the Corporation shall be deemed to receive the minimum amount of consideration without reference to such clause;

(B) With respect to any Convertible Securities issued after the Issuance Date for which an adjustment to the Conversion Price previously has been made pursuant to Section 6(b)(ii) of this Article IX, upon any increase in the number of shares of Common Stock deliverable upon exercise, conversion or exchange of, or a decrease in the exercise price of, such Convertible Securities other than a change resulting from the anti-dilution provisions thereof, the applicable Conversion Price shall forthwith be readjusted retroactively to give effect to such increase or decrease;

(C) With respect to any Convertible Securities issued after the Issuance Date for which an adjustment to the Conversion Price has previously not been made pursuant to Section 6(b)(ii) of this Article IX, if there is any increase in the number of shares of Common Stock deliverable upon exercise, conversion or exchange of, or a decrease in the exercise price of, such Convertible Securities other than a change resulting from the anti-dilution provisions thereof, such Convertible Securities shall be treated as if they had been cancelled and reissued and an adjustment to the Conversion Price with respect to such deemed issuance shall be made pursuant to Section 6(b)(ii) of this Article IX, if applicable;

(D) With respect to any Convertible Securities issued prior to the Issuance Date, if there is any increase in the number of shares of Common Stock deliverable upon exercise, conversion or exchange of, or a decrease in the exercise price of, such Convertible Securities other than a change resulting from the anti-dilution provisions thereof, such Convertible Securities shall be treated as if they had been cancelled and reissued and an adjustment to the Conversion Price with respect to such deemed issuance shall be made pursuant to Section 6(b)(ii) of this Article IX, if applicable;

(E) No further adjustment of the Conversion Price adjusted upon the issuance of any such Convertible Securities shall be made as a result of the actual issuance of Common Stock upon the exercise, conversion or exchange of any such Convertible Securities; and

(F) On the expiration or termination of any Convertible Securities, the Conversion Price shall forthwith be recalculated to such Conversion Price as would have been calculated had the adjustment been made upon the basis of the issuance of only the number of shares or Common Stock actually issued upon the exercise, conversion or exchange of such Convertible Securities (but taking into account other adjustments (or potential adjustments) made following the time of issuance of such Convertible Securities).

(iv) *Rights Distributions.* No adjustment of the Conversion Price

pursuant to Section 6(b)(ii) of this Article IX shall be made as the result of the adoption of a plan commonly referred to as a "Stockholders' Rights Plan" which provides for the issuance of rights to acquire shares of capital stock of the Corporation upon the occurrence of some event that is not within the control of the rights holders, or the issuance of rights under such plan; provided, however, that the issuance of capital stock of the Corporation pursuant to such rights shall require adjustment to the Conversion Price pursuant to Section 6(b)(ii) of this Article IX.

(v) *Calculations.* All calculations of the Conversion Price shall be made to the nearest four decimal places. Anything in Section 6(b) of this Article IX to the contrary notwithstanding, in no event shall the then current Conversion Price be increased as a result of any calculation made at any time pursuant to Section 6(b)(ii) of this Article IX. No adjustment to the Conversion Price pursuant to Section 6(b) of this Article IX shall be required unless such adjustment would require an increase or decrease of at least 1% in the Conversion Price; provided, however, that any adjustments which by reason of this Section 6(b)(v) are not required to be made shall be carried forward and taken into account in any subsequent adjustment.

(vi) *Outstanding Shares.* The number of shares of Common Stock at any time outstanding shall include all shares of Common Stock outstanding at such time and any shares of Common Stock issuable upon conversion or exercise of or in exchange for any Convertible Securities to the extent any such Convertible Securities are (i) convertible, exercisable or exchangeable at such time and (ii) convertible, exercisable, or exchangeable at a price that is less than the Fair Market Value of a share of Common Stock issuable upon such conversion, exercise or exchange at such time. The number of shares of Common Stock at any time outstanding shall not include any shares of Common Stock then owned or held by or for the account of the Corporation or any Subsidiary of the Corporation, and the disposition of any shares owned or held by the Corporation or any Subsidiary of the Corporation to any Person other than the Corporation or any Subsidiary of the Corporation shall be considered an issuance or sale of Common Stock.

(vii) *Successive Adjustments.* Successive adjustments in the Conversion Price shall be made, without duplication, whenever any event specified in Section 6(b)(i) or Section 6(b)(ii) of this Article IX shall occur.

(c) Reorganization, Consolidation, Merger, Asset Sale.

(i) In case of any capital reorganization or reclassification of outstanding shares of Common Stock (other than a reclassification covered by Section 6(b) of this Article IX), or in case of any consolidation or merger of the Corporation with or into another Person, or in case of any sale, lease, exchange, transfer, conveyance or other disposition (other than by way of merger or consolidation) of all or substantially all of the Corporation's assets, on a consolidated basis, in one transaction or a series of related transactions, to any Person (including any group that is deemed to be a Person) (each or the foregoing being referred to as a "Series B Transaction"), in each case which is effected in such a manner that the holders of Common Stock are entitled to receive (either directly or upon subsequent liquidation) stock or other securities or property (including cash) with respect to or in exchange for Common Stock, then each share of Series B Preferred Stock then outstanding shall thereafter be convertible into,

in lieu of the Voting Common Stock issuable upon such conversion prior to the consummation of such Series B Transaction, the kind and amount of shares of stock and other securities and property (including cash) receivable upon the consummation of such Series B Transaction by a holder of that number of shares of Voting Common Stock into which one share of Series B Preferred Stock was convertible immediately prior to the consummation of such Series B Transaction (including, on a pro rata basis, the cash, securities or property received by holders of Common Stock in any tender or exchange offer that is a step in such Series B Transaction); provided that if the Series B Preferred Stock becomes convertible into property, then such conversion shall be out of funds legally available therefor; and provided, further, that, in any Series B Transaction where a holder effectuates a conversion pursuant to this Section 6(c), such holder shall not be entitled to receive any payment of Liquidation Preference pursuant to Section 4 of this Article IX (it being understood that where both Section 4 of this Article IX and this Section 6(c) are applicable to a Series B Transaction, the Corporation shall give each holder of the Series B Preferred Stock the right to elect whether to receive the Liquidation Preference pursuant to Section 4 of this Article IX or to receive, upon conversion of the Series B Preferred Stock, the kind and amount of shares of stock and other securities and property referred to in the immediately preceding sentence). In any such case, the Corporation or the Person formed by the consolidation or resulting from the merger or which acquires such assets or which acquires the Corporation's shares, as the case may be, shall make appropriate provisions in its certificate of incorporation or other constituent document and in the definitive transaction documents relating to the Series B Transaction as to the rights and interest thereafter of the holder of shares of Series B Preferred Stock, to the end that the provisions set forth herein (including provisions with respect to changes in and other adjustments of the number of shares of Voting Common Stock issuable upon conversion of the Series B Preferred Stock and the Conversion Price) shall thereafter be applicable in relation to any shares of stock or other securities or other property deliverable upon the conversion of the shares of Series B Preferred Stock. The Corporation shall not effect any such Series B Transaction unless prior to or simultaneously with the consummation thereof the surviving corporation or purchaser, as the case may be, shall assume by written instrument the obligation to deliver to each holder of shares of Series B Preferred Stock such shares of stock, securities or other property as, in accordance with the foregoing provisions, such holder is entitled to receive, and shall have delivered such assumption agreement to such holder. In case securities or property other than Common Stock shall be issuable or deliverable upon conversion as aforesaid, then all references to Common Stock in this Section 6 shall be deemed to apply, so far as appropriate and as nearly as may be, to such other securities or property. The provisions of this Section 6(c) shall similarly apply to successive Series B Transactions. The Corporation shall give written notice to the holders of Series B Preferred Stock at least 20 Business Days prior to the date on which any Series B Transaction or similar transaction affecting the Corporation shall take place.

(ii) Nothing contained in this Section 6(c) shall limit the rights of holders of the Series B Preferred Stock to convert the Series B Preferred Stock or to vote their shares of Series B Preferred Stock in connection with a Series B Transaction.

(d) Reports. Whenever the number of shares of Voting Common Stock into which each share of Series B Preferred Stock is convertible is adjusted as provided in this Section 6, the Corporation shall promptly mail to the holders of record of the outstanding shares of Series B Preferred Stock, at their respective addresses as the same shall appear in the

Corporation's transfer books, a certificate signed by an executive officer of the Corporation stating that the number of shares of Voting Common Stock into which the shares of Series B Preferred Stock are convertible has been adjusted (setting forth in reasonable detail and certifying the calculation of such adjustment), the new number of shares of Voting Common Stock (or describing the new stock, securities, cash or other property) into which each share of Series B Preferred Stock is convertible as a result of such adjustment, a brief statement of the facts requiring such adjustment and when such adjustment became effective.

(e) Conversion Procedures.

(i) The holder of any shares of Series B Preferred Stock may exercise its right to convert any or all such outstanding shares into shares of Voting Common Stock at any time by surrendering for such purpose to the Corporation, at its principal office or at such other office or agency maintained by the Corporation for that purpose, a certificate or certificates representing the shares of Series B Preferred Stock to be converted, duly endorsed in blank, accompanied by a written notice stating that such holder elects to convert all or a specified number of such shares in accordance with the provisions of this Section 6.

(ii) As promptly as practicable, and in any event within two Business Days after the surrender of such certificate or certificates and the receipt of such notice relating thereto, the Corporation shall deliver or cause to be delivered (x) certificates (which shall bear legends, if appropriate) registered in the name of such holder representing the number of shares of Voting Common Stock to which the holder of shares of Series B Preferred Stock so converted shall be entitled, (y) if less than the full number of shares of Series B Preferred Stock evidenced by the surrendered certificate or certificates are being converted, a new certificate or certificates for the number of shares evidenced by such surrendered certificate or certificates less the number of shares converted and (z) payment of all amounts to which a holder is entitled pursuant to Sections 6(a)(i) and 6(f) of this Article IX. All shares of Voting Common Stock issuable upon conversion of the Series B Preferred Stock shall be issued without charge to the holders of Series B Preferred Stock and upon issuance shall be fully paid and non-assessable, free and clear of all taxes, liens, charges and encumbrances created, in each case, by the Corporation with respect to the issuance thereof. Such conversion shall be deemed to have been made at the close of business on the date of receipt of such notice and of such surrender of the certificate or certificates representing the shares of Series B Preferred Stock to be converted so that the rights of the holder thereof as to the shares being converted shall cease except for the right to receive shares of Voting Common Stock and any payment of amounts due pursuant to Sections 6(a)(i) and 6(f) of this Article IX, and the Person entitled to receive the shares of Voting Common Stock shall be treated for all purposes as having become the record holder of such shares of Voting Common Stock at such time.

(iii) If a conversion of Series B Preferred Stock is to be made in connection with an Initial Public Offering (subject to Section 6(a)(ii) of this Article IX), a Series B Transaction or a similar transaction affecting the Corporation (other than a tender or exchange offer), the conversion of any shares of Series B Preferred Stock may, at the election of the holder thereof, be conditioned upon the consummation of such transaction, in which case such conversion shall not be deemed to be effective until such transaction has been consummated. In connection with any tender or exchange offer for shares of Common Stock, holders of Series B

Preferred Stock shall have the right to tender (or submit for exchange) shares of Series B Preferred Stock in such a manner so as to preserve the status of such shares as Series B Preferred Stock until immediately prior to such time as shares of Common Stock are to be purchased (or exchanged) pursuant to such offer, at which time that portion of the shares of Series B Preferred Stock so tendered (or submitted for exchange) which is convertible into the number of shares of Voting Common Stock to be purchased (or exchanged) pursuant to such offer shall be automatically converted into the appropriate number of shares of Voting Common Stock. Any shares of Series B Preferred Stock not so converted shall be returned to the holder as Series B Preferred Stock.

(iv) The Corporation shall not close its books against the transfer of Series B Preferred Stock or of Voting Common Stock issued or issuable upon conversion of Series B Preferred Stock in any manner which interferes with the timely conversion of Series B Preferred Stock.

(v) In the event of an automatic conversion of the Series B Preferred Stock pursuant to Section 6(a)(ii) of this Article IX, each holder of shares of Series B Preferred Stock shall surrender for such purpose to the Corporation, at its principal office or at such other office or agency maintained by the Corporation for that purpose, the certificate or certificates representing the shares of Series B Preferred Stock held by such holder, duly endorsed in blank. As promptly as practicable after the surrender of such certificate or certificates and consummation of the Initial Public Offering, and, provided that such holder has effected such surrender at least 10 Business Days following the receipt by it of the notice referred to in Section 6(a)(ii) of this Article IX, in sufficient time to allow such holder to participate in the Initial Public Offering, if such holder is participating, the Corporation shall deliver or cause to be delivered (x) certificates (which shall bear legends, if appropriate) registered in the name of such holder representing the number of shares of Voting Common Stock to which such holder shall be entitled, and (y) payment of all amounts to which such holder is entitled pursuant to Sections 6(a)(ii) and 6(f) or this Article IX. All shares of Voting Common Stock issuable upon conversion of the Series B Preferred Stock shall be issued without charge to the holders of Series B Preferred Stock and upon issuance shall be fully paid and non-assessable, free and clear of all taxes, liens, charges and encumbrances created, in each case, by the Corporation with respect to the issuance thereof. Such conversion shall be deemed to have been made immediately prior to (but contingent upon) the consummation of the Initial Public Offering, so that, upon the consummation or the Initial Public Offering, the rights of the holder thereof shall cease except for the right to receive shares of Voting Common Stock and any payment of amounts due pursuant to Sections 6(a)(ii) and 6(f) of this Article IX, and the Person entitled to receive the shares of Voting Common Stock shall be treated for all purposes as having become the record holder of such shares of Voting Common Stock at such time.

(f) Fractional Shares. In connection with the conversion of any shares of Series B Preferred Stock pursuant to this Section 6, no fractions of shares of Voting Common Stock shall be issued, but in lieu thereof the Corporation shall pay a cash adjustment in respect of such fractional interest in an amount equal to such fractional interest multiplied by the Fair Market Value of a share of Voting Common Stock on the day on which such shares of Series B Preferred Stock are deemed to have been converted. If more than one share of Series B Preferred Stock shall be surrendered for conversion at one time by the same holder, the number of full

shares of Voting Common Stock issuable upon conversion thereof shall be computed on the basis of the total number of shares of Series B Preferred Stock so surrendered.

(g) Reservation of Shares. The Corporation shall at all times reserve and keep available, free from liens, charges and security interests and not subject to any preemptive rights, for issuance upon conversion of the Series B Preferred Stock, such number of its authorized but unissued shares of Voting Common Stock as will from time to time be sufficient to permit the conversion of all outstanding shares of Series B Preferred Stock, and shall take or cause to be taken all action required to increase the authorized number of shares of Voting Common Stock if necessary to permit the conversion of all outstanding shares of Series B Preferred Stock and to ensure that the shares of Voting Common Stock may be issued without violation of any applicable law or regulation or of any requirement of any securities exchange or inter-dealer quotation system of which the shares of Voting Common Stock may be listed or traded.

(h) Certain Events. If any event occurs as to which the foregoing provisions of this Section 6 are not strictly applicable or, if strictly applicable, would not, in the good faith judgment of the Board of Directors, fairly protect the conversion rights of the Series B Preferred Stock in accordance with the essential intent and principles of such provisions, then the Board of Directors shall make such adjustments in the application of such provisions, in accordance with such essential intent and principles, as shall be reasonably necessary, in the good faith opinion of the Board of Directors, to protect such conversion rights as aforesaid, but in no event shall any such adjustment have the effect of increasing the Conversion Price, or otherwise adversely affect the holders of Series B Preferred Stock.

SECTION 7. REACQUIRED SHARES.

Any shares of Series B Preferred Stock converted, purchased or otherwise acquired by the Corporation in any manner whatsoever shall have the status of authorized but unissued shares of Preferred Stock of the Corporation, without designation as to series, subject to reissuance by the Board of Directors as shares of anyone or more series.

ARTICLE X
SERIES C PREFERRED STOCK

SECTION 1. RANK.

The Series C Preferred Stock shall rank senior to the Common Stock, but junior to the Series A Preferred Stock, the Series B Preferred Stock and all other capital stock of the Corporation, with respect to rights on Liquidation. The C-1 Preferred, the C-2 Preferred, the C-3 Preferred and the C-4 Preferred shall rank on parity with one another with respect to rights on Liquidation.

SECTION 2. DIVIDENDS.

The Series C Preferred Stock shall not be entitled to receive any dividends from the Corporation.

SECTION 3. REDEMPTION.

The Corporation shall have no right to redeem any shares of Series C Preferred Stock, nor shall any holder thereof have the right to require the Corporation to redeem any such share.

SECTION 4. LIQUIDATION, DISSOLUTION OR WINDING UP.

(a) In the event of a Liquidation, each holder of shares of C-1 Preferred, C-2 Preferred, C-3 Preferred or C-4 Preferred shall be entitled to receive out of assets of the Corporation available for distribution to its stockholders, in preference to any distribution to holders of securities that are Junior Securities with respect to a Liquidation, an amount of cash with respect to each share of C-1 Preferred, C-2 Preferred, C-3 Preferred or C-4 Preferred held by such holder equal to the Liquidation Preference.

(b) No payment of the Liquidation Preference shall be made with respect to any share of C-1 Preferred, C-2 Preferred, C-3 Preferred or C-4 Preferred unless and until the liquidation preferences payable with respect to any securities that are Senior Securities with respect to payments upon a Liquidation shall have been paid in full. No full preferential payment on account of any Liquidation shall be made with respect to any class of securities that are Parity Securities with respect to payments upon a Liquidation unless the Liquidation Preference in respect of each share of Series C Preferred Stock shall likewise be paid at the same time in connection with such Liquidation. If, upon any Liquidation, after the distribution of the liquidation preferences to any securities that are Senior Securities with respect to payments upon a Liquidation, the assets of the Corporation are not sufficient to pay in full the Liquidation Preference payable with respect to all of the outstanding shares of Series C Preferred Stock and the full liquidation payments payable with respect to any outstanding securities that are Parity Securities with respect to payments upon a Liquidation, then all such shares of Series C Preferred Stock and such Parity Securities shall share ratably in such distribution of assets in accordance with the full respective preferential payments that would be payable on such shares of Series C Preferred Stock and such Parity Securities if all amounts payable thereon were payable in full.

(c) After the payment to the holders of shares of Series C Preferred Stock of the full amount of any liquidating distribution to which they are entitled under this Section 4, the holders of Series C Preferred Stock as such shall have no right or claim to any of the remaining assets of the Corporation.

(d) Without limiting the voting rights, if any, of any holder of Series C Preferred Stock, the Corporation shall give the holders of the Series C Preferred Stock written notice at least 10 Business Days prior to the date on which the Corporation closes its books or takes a record, with respect to any Liquidation.

SECTION 5. VOTING RIGHTS.

(a) General. No holder of Series C Preferred Stock shall be entitled to any voting rights, except as hereinafter provided in this Section 5 or as required by law. Holders of Series C Preferred Stock shall be entitled to notice of all stockholders meetings to the extent provided by, and in accordance with the procedures set forth in the Corporation's bylaws.

(b) Voting Rights for Directors.

(i) The holders of C-1 Preferred, voting separately as a class, shall be entitled to elect to the Board of Directors a total of three individuals (the "C-1 Directors"), with all other stockholders of the Corporation specifically denied the right to nominate and elect the C-1 Directors.

(ii) The holders of C-2 Preferred, voting separately as a class, shall be entitled to elect to the Board of Directors one individual (the "C-2 Director"), with all other stockholders of the Corporation specifically denied the right to nominate and elect the C-2 Director.

(iii) The holders of C-3 Preferred, voting separately as a class, shall be entitled to elect to the Board of Directors one individual (the "C-3 Director"), with all other stockholders of the Corporation specifically denied the right to nominate and elect the C-3 Director.

(iv) The holders of C-4 Preferred, voting separately as a class, shall be entitled to elect to the Board of Directors one individual (the "C-4 Director"), with all other stockholders of the Corporation specifically denied the right to nominate and elect the C-4 Director.

(c) Voting With Respect to Certain Matters. In addition to any matters requiring a separate vote of the Applicable Series of the Series C Preferred Stock under applicable law, the Corporation shall not, without the prior written consent or approval of the holders of more than 50% of the issued and outstanding shares of the Applicable Series of the Series C Preferred Stock:

(i) amend, repeal, or change the rights, preferences or privileges of the shares of the Applicable Series of the Series C Preferred Stock (as in effect on the Issuance Date) in any manner that would affect adversely the shares of the Applicable Series of the Series C Preferred Stock in a manner different from the effect on shares of the other classes or series of capital stock of the Corporation (including maintaining the seniority of the Series C Preferred Stock over certain other classes or series of capital stock of the Corporation, as set forth in the first sentence of Section 1 of this Article X as in effect on the Issuance Date); or

(ii) increase or decrease the total number of authorized shares of the Applicable Series of the Series C Preferred Stock.

(d) Election Procedures.

(i) The right of the respective holders of the Applicable Series of the Series C Preferred Stock to elect directors as described in Section 5(b) of this Article X (including without limitation to fill any vacancy occurring in the office of any director elected pursuant to Section 5(b) of this Article X) may be exercised either at a special meeting of the holders of the Applicable Series of the Series C Preferred Stock, at any annual meeting of stockholders of the Corporation held for the purpose of electing directors, or by the written consent of the holders of the Applicable Series of the Series C Preferred Stock acting without a

meeting pursuant to Section 228 of the General Corporation Law of the State of Delaware. The term of office or any director elected by the holders of the Applicable Series of the Series C Preferred Stock pursuant to Section 5(b) of this Article X shall terminate upon the election of his or her successor or upon his or her earlier death, resignation or removal as provided by Section 5(d)(ii) of this Article X.

(ii) Notwithstanding anything contained in the Certificate of Incorporation or bylaws of the Corporation, any director so elected pursuant to Section 5(b) of this Article X may be removed without cause only by the holders of the Applicable Series of the Series C Preferred Stock with respect which such director was elected. The right of the holders of the Applicable Series of the Series C Preferred Stock to remove directors without cause may be exercised at any special meeting of such holders or by a written consent of such holders acting without a meeting pursuant to Section 228 of the General Corporation Law of the State of Delaware.

(iii) In case of a vacancy occurring in the office of any director so elected pursuant to Section 5(b) of this Article X, for whatever reason, the holders of the Applicable Series of the Series C Preferred Stock with respect which such director was elected may elect a successor to hold office for the unexpired term of such director or, if the vacancy is in the office of a C-1 Director, such vacancy may be filled by a majority of the other C-1 Directors (or by the sole C-1 Director) then in office.

(iv) All actions taken by the holders of the Applicable Series of the Series C Preferred Stock under this Section 5 shall be taken by the affirmative vote, or by written consent, of the holders of more than 50% of the issued and outstanding shares of the Applicable Series of the Series C Preferred Stock.

(e) Number of Votes Per Share. In connection with any right to vote as a single class pursuant to this Section 5, or on any matter required by law, each holder of shares of the Applicable Series of the Series C Preferred Stock shall have one vote for each share held.

SECTION 6. NO CONVERSION.

The shares of Series C Preferred Stock shall not be convertible into Common Stock or any other security of the Corporation.

SECTION 7. REACQUIRED SHARES.

Any shares of Series C Preferred Stock purchased or otherwise acquired by the Corporation in any manner whatsoever shall have the status of authorized but unissued shares of Preferred Stock of the Corporation, without designation as to series, subject to reissuance by the Board of Directors as shares of anyone or more series.

ARTICLE XI
BOARD OF DIRECTORS

SECTION 1. MANAGEMENT.

The business and affairs of the Corporation shall be managed by or under the direction of the Board of Directors. The Board of Directors may exercise all such authority and powers of the Corporation and do all such lawful acts and things as are not by statute or this Certificate of Incorporation directed or required to be exercised or done by the stockholders.

SECTION 2. NUMBER OF DIRECTORS.

The number of directors of the Corporation shall initially be fixed by the Board of Directors at not more than 10. The number of directors of the Corporation shall be fixed from time to time exclusively by the Board of Directors as set forth in this Section 2. The Board of Directors may, by resolution of the Board of Directors, (i) decrease the number of directors comprising the Board of Directors, but not below the number of directors then in office and not below the number that would prevent the holders of any Applicable Series of the Series C Preferred Stock from electing their Designated Director or Designated Directors, and (ii) increase the number of directors comprising the Board of Directors, in each case by the vote of a majority of the Designated Directors elected by the holders of the C-1 Preferred and the vote of a majority of the other members of the Board of Directors.

SECTION 3. NEWLY-CREATED DIRECTORSHIPS AND VACANCIES.

Subject to the rights of the holders of the Series C Preferred Stock or any other series of Preferred Stock then outstanding, newly created directorships resulting from any increase in the number of directors or any vacancies in the Board of Directors resulting from death, resignation, removal from office or any other cause shall, unless otherwise required by law or resolution of the Board of Directors, be filled only by the Board of Directors by the vote of a majority of the Designated Directors elected by the holders of the C-1 Preferred and the vote of a majority of the other members of the Board of Directors. A director elected to fill a newly created directorship or other vacancy shall hold office until such director's successor has been duly elected or until his or her earlier death, resignation or removal as provided in this Certificate of Incorporation.

SECTION 4. REMOVAL OF DIRECTORS.

Subject to the rights of the holders of the Series C Preferred Stock or any other series of Preferred Stock then outstanding, any director may be removed, with or without cause, from office at any time by the affirmative vote of the holders of a majority of the voting power of the issued and outstanding shares of Voting Common Stock and the issued and outstanding shares of Preferred Stock entitled to vote generally with the Voting Common Stock on all matters all which the holders of Voting Common Stock are entitled to vote, voting together as a single class; provided, however, that any Designated Director may only be removed without cause by the vote of the holders of more than 50% of the issued and outstanding shares of the Applicable Series of the Series C Preferred Stock, voting as a separate class.

SECTION 5. WRITTEN BALLOT NOT REQUIRED.

Elections of directors need not be by written ballot unless the bylaws of the

Corporation shall otherwise provide.

SECTION 6. BYLAWS.

The Board of Directors is expressly authorized to adopt, amend or repeal the bylaws or the Corporation. Any bylaws made by the directors under the powers conferred hereby may be amended or repealed by the Board of Directors or by the stockholders of the Corporation. The stockholders shall also have power to adopt, amend or repeal the bylaws of the Corporation; provided, however, that, in addition to any vote of the holders of any class or series of capital stock of the Corporation required by law, by this Certificate of Incorporation or by the bylaws, the affirmative vote of the holders of more than 50% of the voting power of the issued and outstanding shares of Voting Common Stock and the issued and outstanding shares of Preferred Stock entitled to vote generally with the Voting Common Stock on all matters on which the holders of Voting Common Stock are entitled to vote, voting together as a single class, shall be required to adopt, amend or repeal any provision of the bylaws of the Corporation,

ARTICLE XII
LIMITATION OF LIABILITY; INDEMNIFICATION

A director of the Corporation shall not be personally liable to the Corporation or its stockholders for monetary damages for breach of fiduciary duty as a director; provided, however, that the foregoing shall not eliminate or limit the liability of a director (i) for any breach of the director's duty of loyalty to the Corporation or its stockholders, (ii) for acts or omissions not in good faith or which involve intentional misconduct or a knowing violation of law, (iii) under Section 174 of the DGCL or (iv) for any transaction from which the director derived an improper personal benefit. If the DGCL is hereafter amended to permit further elimination or limitation of the personal liability of directors, then the liability of a director of the Corporation shall be eliminated or limited to the fullest extent permitted by the DGCL as so amended.

The Corporation shall, to the fullest extent permitted by applicable law, indemnify and advance expenses to each director and officer of the Corporation. The Corporation may indemnify and advance expenses to each employee and agent of the Corporation, and any other Person whom the Corporation is authorized to indemnify under the provisions of the DGCL, as provided in the bylaws or the Corporation.

Any amendment, repeal or modification of the foregoing provisions of this Article XII shall not adversely affect any right or protection of any director, officer or other agent of the Corporation existing all the time of, or increase the liability of any director, officer or other agent of the Corporation with respect to any acts or omissions of such director, officer or other agent occurring prior to, such amendment, repeal or modification.

ARTICLE XIII
AMENDMENT

The Corporation reserves the right to amend, change or repeal any provision contained in this Certificate of Incorporation, in the manner now or hereafter prescribed by statute, and all rights conferred upon stockholders herein are granted subject to this reservation.

Notwithstanding any other provision of this Certificate of Incorporation or the bylaws of the Corporation, and notwithstanding the fact that a lesser percentage or separate class vote may be specified by law, this Certificate of Incorporation, the bylaws of the Corporation or otherwise, but in addition to any affirmative vote of the holders of any particular class or series of the capital stock required by law, this Certificate of Incorporation, the bylaws of the Corporation or otherwise, the affirmative vote of the holders of more than 50% of the voting power of the issued and outstanding shares of Voting Common Stock and the issued and outstanding shares of Preferred Stock entitled to vote generally with the Voting Common Stock on all matters on which the holders of Voting Common Stock are entitled to vote, voting together as a class, shall be required to adopt any provision inconsistent with, or to amend or repeal any provision of, Articles XII or XIII of this Certificate of Incorporation.

ARTICLE XIV
NO IMPAIRMENT

The Corporation will not amend its Certificate of Incorporation or reorganize, transfer assets, consolidate, merge, dissolve, or voluntarily effect any other transaction, the sole purpose of which is to avoid the observance or performance of any of the terms to be observed or performed hereunder by the Corporation.

ARTICLE XV
PROPERTY OF STOCKHOLDERS

Except as otherwise provided by applicable law, the private property or assets of the stockholders of the Corporation shall not to any extent whatsoever be subject to the payment of the debts of the Corporation.

ARTICLE XVI
DEFINITIONS; HEADINGS

(a) For the purposes of this Certificate of Incorporation, the following definitions shall apply:

"Additional Shares" has the meaning set forth in Section 6(b)(ii) of Article VIII.

"Applicable Series of the Series C Preferred Stock" means the C-1 Preferred, the C-2 Preferred, the C-3 Preferred or the C-4 Preferred, as applicable.

"Approved Options" means (1) options to purchase up to 8,058,834 shares of Common Stock granted under the Corporation's 2007 Stock Option Plan as in effect on the Issuance Date (or as such Plan may be amended upon receipt of the Requisite Approval), which grants received the Requisite Approval, and (2) any options to purchase or other rights to acquire shares of Common Stock granted under any other equity incentive plan, the adoption of which received the Requisite Approval and which grants received the Requisite Approval.

"Arbiter" shall have the meaning ascribed to such term in the definition of "Fair Market Value."

"Attribute" has the meaning set forth in Section I of Article VIII.

"Beneficially Owned" shall mean beneficially owned as determined in accordance with Securities Exchange Act Rule 13d-3.

"Board of Directors" means the Board of Directors of the Corporation.

"Business Day" means any day other than a Saturday, Sunday, or a day on which commercial banks in the City of New York are authorized or obligated by law or executive order to close.

"Certificate of Incorporation" means the Certificate of Incorporation of the Corporation, as amended from time to time.

"Closing Price" has the meaning set forth in the definition of "Fair Market Value."

"Common Stock" means the Voting Common Stock and the Non-Voting Common Stock or either of them.

"Conversion Price" means, with respect to the Series A Preferred Stock, $1.00, subject to adjustment as provided in Section 6 of Article VIII, and, with respect to the Series B Preferred Stock, $4.6346, subject to adjustment as provided in Section 6 of Article IX.

"Convertible Securities" means (i) any options or warrants to purchase or other rights to acquire Common Stock, (ii) any securities by their terms convertible into, or exercisable or exchangeable for, Common Stock (directly or indirectly) and (iii) any options or warrants to purchase or other rights to acquire any such convertible, exercisable or exchangeable securities.

"Designated Director" means a member of the Board of Directors that was elected exclusively by the vote of one of the Applicable Series of the Series C Preferred Stock.

"Excluded Issuances" means the issuance of any shares of Common Stock or Convertible Securities (whether treasury shares or newly issued shares) (1) pursuant to a dividend or distribution on, or a subdivision, combination or reclassification of, the outstanding shares of Common Stock which, in the case of the Series A Preferred Stock, requires an adjustment in the Conversion Price pursuant to Section 6(b)(i) of Article VIII, and, in the case of the Series B Preferred Stock, requires an adjustment in the Conversion Price pursuant to Section 6(b)(i) of Article IX, (2) upon the exercise or conversion of any Convertible Securities issued on, or outstanding as of, the Issuance Date, including the Series A Preferred Stock and the Series B Preferred Stock, except, in the case of the Series A Preferred Stock, as contemplated by Section 6(b)(iii)(5)(D) of Article VIII and, in the case of the Series B Preferred Stock, as contemplated by Section 6(b)(iii)(5)(D) of Article IX, (3) pursuant to the grant or exercise of any Approved Options, (4) as consideration for the acquisition by the Corporation of another business entity or interest therein (including a joint venture or strategic alliance) by merger, stock purchase, purchase of substantially all the assets or other business combination or investment, in each case, which received the Requisite Approval, or (5) pursuant to Section 2.3 of the Preferred Stock Purchase Agreement.

"Fair Market Value" means, with respect to any security as of any date, if such security is listed or traded in a manner referred to below, an amount equal to the average of the daily Closing Prices on the twenty consecutive Trading Days immediately preceding such date. As used in this Certificate of Incorporation, the term "Closing Price", on any day, shall mean the last reported sales price on such day or, in the event no such sale takes place on such day, the average of the closing bid and asked prices, in each case on the New York Stock Exchange or, if such security is not then listed or admitted to trading on such exchange, on the principal national securities exchange on which such security is listed or admitted to trading, or, if such security is not listed or admitted to trading on any such exchange, the average of the highest reported bid and lowest reported asked prices as furnished by the National Association of Securities Dealers through the National Association of Securities Dealers Automated Quotation System ("Nasdaq") (or a similar organization if Nasdaq is no longer reporting such information). If such security is not listed and traded in a manner that the pricing information referred to above is available for the period required hereunder, or with respect to an asset other than a security (and other than cash which shall be valued at its face amount), the Fair Market Value of such security or asset shall be determined by mutual agreement between the Corporation (acting through the Board of Directors) and the holders of a majority of the outstanding shares of Series A Preferred Stock and the holders of a majority of the Series B Preferred Stock (considered as a single class, with each share of Series A Preferred Stock and each share of Series B Preferred Stock having the number or votes equal to the number of shares of Voting Common Stock into which such share of Series A Preferred Stock or Series B Preferred Stock, as applicable, may be converted) or, if the parties are unable to agree within 10 Business Days following the Corporation's written request to the holders of the Series A Preferred Stock and the holders of the Series B Preferred Stock that agreement thereon be reached, then as determined by an independent investment banking firm or valuation firm (an "Arbiter") selected by mutual agreement between the Corporation and the holders of a majority of the outstanding shares of Series A Preferred Stock and the holders of a majority of the outstanding shares of Series B Preferred Stock (determined as set forth above) (or, if the parties are unable to agree on an Arbiter within 10 Business Days of the Corporation's written request to the holders of the Series A Preferred Stock and the holders of the Series B Preferred Stock that agreement thereon be reached, then by an Arbiter selected by the New York City office of the American Arbitration Association) (with the Corporation, on the one hand, and the holders of the Series A Preferred Stock and the holders of the Series B Preferred Stock, on the other hand, each bearing one half of the fees and expenses of the Arbiter). Notwithstanding the foregoing, the determination of the Fair Market Value of a share of Voting Common Stock for purposes of Section 6(f) of Article VIII or Section 6(f) of Article IX, as applicable, shall be made by the Board of Directors, which determination shall be final and binding.

"Initial Public Offering" means the first public offering of shares of Common Stock.

"Investor Stockholders Agreement" means the Investor Stockholders Agreement, dated March 28, 2007, by and among the Corporation, the holders of the Series A Preferred Stock and the holders of the Series B Preferred Stock, as such agreement may be amended from time to time as provided in such agreement. A copy of the Investor Stockholders Agreement will be made available without charge to any stockholder upon request.

"Issuance Date" means March 28, 2007.

"Junior Securities" means:

(1) with respect to the Series A Preferred Stock, each class or series of capital stock of the Corporation now or hereafter authorized, issued or outstanding which by its terms expressly provides that it will rank junior to the Series A Preferred Stock, or which does not specify its rank, with respect to one or both of the following Attributes: (i) payment of dividends and distributions and (ii) the distribution of assets upon Liquidation;

(2) with respect to the Series B Preferred Stock, each class or series of capital stock of the Corporation now or hereafter authorized, issued or outstanding which by its terms expressly provides that it will rank junior to the Series B Preferred Stock, or which does not specify its rank, with respect to one or both of the following Attributes: (i) payment of dividends and distributions and (ii) the distribution of assets upon Liquidation; and

(3) with respect to the Series C Preferred Stock, each class or series of capital stock of the Corporation now or hereafter authorized, issued or outstanding which by its terms expressly provides that it will rank junior to the Series C Preferred Stock with respect to the distribution of assets upon Liquidation.

This definition of Junior Securities shall include any Convertible Securities exercisable or exchangeable for or convertible into any Junior Securities.

"Liquidation" has the meaning set forth in Section 4(a) of Article VIII.

"Liquidation Preference" means:

(1) with respect to a share of Series A Preferred Stock, the greater of (x) the sum of (i) the Stated Value plus (ii) an amount, if any, equal to the aggregate of any dividends declared but not yet paid on such share of Series A Preferred Stock and (y) the amount that would be payable in the Liquidation in respect of the Voting Common Stock issuable upon conversion of such share of Series A Preferred Stock if all outstanding shares of Series A Preferred Stock were converted into Voting Common Stock immediately prior to the Liquidation in accordance with Section 6 of Article VIII;

(2) with respect to a share of Series B Preferred Stock, the greater of (x) the sum of (i) the Stated Value plus (ii) an amount, if any, equal to the aggregate of any dividends declared but not yet paid on such share of Series B Preferred Stock and (y) the amount that would be payable in the Liquidation in respect of the Voting Common Stock issuable upon conversion of such share of Series B Preferred Stock if all outstanding shares of Series B Preferred Stock were converted into Voting Common Stock immediately prior to the Liquidation in accordance with Section 6 of Article IX; and

(3) with respect to a share of Series C Preferred Stock, $1.00 (as adjusted for any split, subdivision, combination, consolidation, recapitalization or similar event with respect to the Applicable Series of the Series C Preferred Stock).

"Nasdaq" has the meaning set forth in the definition of "Fair Market Value".

"Parity Securities" means:

(1) with respect to the Series A Preferred Stock, each class or series of capital stock of the Corporation now or hereafter authorized, issued or outstanding which by its terms expressly provides that it will rank on a parity with the Series A Preferred Stock with respect to one or both of the following Attributes: (i) payment of dividends and distributions and (ii) the distribution of assets upon any Liquidation;

(2) with respect to the Series B Preferred Stock, each class or series of capital stock of the Corporation now or hereafter authorized, issued or outstanding which by its terms expressly provides that it will rank on a parity with the Series B Preferred Stock with respect to one or both of the following Attributes: (i) payment of dividends and distributions and (ii) the distribution of assets upon any Liquidation; and

(3) with respect to the Series C Preferred Stock, each class or series of capital stock of the Corporation now or hereafter authorized, issued or outstanding which by its terms expressly provides that it will rank on a parity with the Series C Preferred Stock with respect to the distribution of assets upon any Liquidation.

This definition of Parity Securities shall include any Convertible Securities exercisable or exchangeable for or convertible into any Parity Securities.

"Person" means an individual, partnership, corporation, limited liability company or partnership, unincorporated organization, trust or joint venture, or a governmental agency or political subdivision thereof or other entity of any kind.

"Preferred Stock Purchase Agreement" means the Preferred Stock Purchase Agreement, dated as of February 22, 2007, by and among the Corporation, Ikaria, Inc. and purchasers of the Series B Preferred Stock, as such agreement may be amended from time to time as provided in such agreement. A copy of the Preferred Stock Purchase Agreement will be made available without charge to any stockholder upon request.

"Requisite Approval" means the approval of the Board of Directors and, if required by one or more of Sections 4.1, 4.2, 4.3, 4.4 and 4.5 of the Investor Stockholders Agreement, the approval or approvals set forth in the applicable Section or Sections of the Investor Stockholders Agreement.

"Senior Securities" means:

(1) with respect to the Series A Preferred Stock, each class or series of capital stock of the Corporation now or hereafter authorized, issued or outstanding which by its terms expressly provides that it will rank senior to the Series A Preferred Stock with respect to one or both of the following Attributes: (i) payment of dividends and distributions and (ii) the distribution of assets upon any Liquidation;

(2) with respect to the Series B Preferred Stock, each class or series of capital stock of the Corporation now or hereafter authorized, issued or outstanding which by its terms expressly provides that it will rank senior to the Series B Preferred Stock with respect to

one or both of the following Attributes: (i) payment of dividends and distributions and (ii) the distribution of assets upon any Liquidation; and

(3) with respect to the Series C Preferred Stock, each class or series of capital stock of the Corporation now or hereafter authorized, issued or outstanding which by its terms expressly provides that it will rank senior to the Series C Preferred Stock with respect to the distribution of assets upon any Liquidation.

This definition of Senior Securities shall include any Convertible Securities exercisable or exchangeable for or convertible into any Senior Securities.

"Series A Transaction" has the meaning set forth in Section 6(c)(i) of Article VIII.

"Series B Transaction" has the meaning set forth in Section 6(c)(i) of Article IX.

"Stated Value" means, with respect to a share of Series A Preferred Stock, $1.00 (as adjusted for any split, subdivision, combination, consolidation, recapitalization or similar event with respect to the Series A Preferred Stock) and, with respect to a share of Series B Preferred Stock, $4.6346 (as adjusted for any split, subdivision, combination, consolidation, recapitalization or similar event with respect to the Series B Preferred Stock).

"Subsidiary" of any Person means any corporation or other entity of which a majority of the voting power of the voting equity securities or equity interest is owned, directly or indirectly, by such Person.

"Trading Day" means a day on which the principal national securities exchange on which the Common Stock is quoted, listed or admitted to trading is open for the transaction of business.

(b) The headings of the sections, paragraphs, subparagraphs, clauses and sub-clauses included in this Certificate of Incorporation are for convenience of reference only and shall not define, limit or affect any of the provisions hereof.

IN WITNESS WHEREOF, this Restated Certificate of Incorporation, which restates and integrates and further amends the provisions of the Certificate of Incorporation of this Corporation, and which has been duly adopted in accordance with Sections 242 and 245 of the Delaware General Corporation Law, has been executed by its duly authorized officer this 7th day of May, 2010.

IKARIA HOLDINGS, INC.

Matthew M. Bennett

Name: Matthew M. Bennett
Title: Senior Vice President and Secretary

PATENT ASSIGNMENT

WHEREAS, IKARIA, INC., a Delaware corporation, having a place of business at Perryville III, Corporate Park, 53 Frontage Road, Hampton, NJ ("ASSIGNOR"), is the owner of the entire right, title and interest in and to the inventions and improvements disclosed in the United States patent applications listed in the attached Schedule A (the "PATENT APPLICATIONS"), including the PATENT APPLICATIONS themselves, all previously-filed international and foreign patents and patent applications claiming priority to one or more of the PATENT APPLICATIONS or to a parent application of any of the PATENT APPLICATIONS, and any as-yet unfiled patents and applications claiming such inventions and improvements and claiming priority to one or more of the PATENT APPLICATIONS or to a parent application of any of the PATENT APPLICATIONS (all of which are collectively referred to as the "PATENT RIGHTS");

WHEREAS, INO THERAPEAUTICS LLC, a Delaware corporation, having a place of business at Perryville III, Corporate Park, 53 Frontage Road, Hampton, NJ ("ASSIGNEE"), is desirous of obtaining the entire right, title and interest in and to the PATENT RIGHTS;

NOW, THEREFORE, for good and valuable consideration, the receipt and sufficiency of which are hereby acknowledged, ASSIGNOR hereby assigns to ASSIGNEE all of its right, title and interest in and to the PATENT RIGHTS; this assignment including said PATENT RIGHTS, any and all United States, international, and foreign patents, utility patents and models, continuations, continuations-in-part, divisionals, reexaminations, reissues, and design registrations granted for any of said inventions or improvements, and the right to claim priority based on the respective filing dates of the PATENT APPLICATIONS and/or their parent application(s) under the International Convention for the Protection of Industrial Property, the Patent Cooperation Treaty, the European Patent Convention, and all other treaties of like purposes; and this assignment also including, without limitation, any claims (known or unknown, suspected or unsuspected) of any nature that ASSIGNOR has or may have against any party for infringement of any of the PATENT RIGHTS, and the right to sue for past infringement and to recover and retain damages and profits in respect thereof; and

ASSIGNOR authorizes the ASSIGNEE to apply in all countries in ASSIGNOR'S name or in its own name or the inventors' names for patents, utility models, design registrations, and like rights of exclusion and for inventors' certificates for said inventions and improvements; and

ASSIGNOR hereby covenants and agrees that ASSIGNOR will communicate to the ASSIGNEE or nominees all facts known to ASSIGNOR pertaining to said inventions and improvements, and ASSIGNOR agrees for itself and its heirs, legal representatives, and assigns, without further compensation to perform such lawful acts and to sign such further applications, assignments, reissues, Preliminary Statements, and other lawful documents, testify in all legal proceedings, make all rightful oaths and declarations, and in general perform or cause to be performed all lawful acts necessary or proper to aid the ASSIGNEE or nominees in obtaining, maintaining, and enforcing all lawful patent protection for the inventions and improvements in the United States and in foreign countries; and

ASSIGNOR hereby covenants that ASSIGNOR has the full right to convey ASSIGNOR'S entire right, title, and interest herein assigned and that ASSIGNOR has not executed and will not execute any agreement in conflict herewith.

IN TESTIMONY WHEREOF, ASSIGNOR has caused this Assignment to be executed by its duly authorized officer.

IKARIA, INC.

By William Schmidt

Title Assistant Secretary

Date August 20, 2012

Daria Cooney

DARIA COONEY
NOTARY PUBLIC
WARREN COUNTY, NJ.
MY COMMISION EXPIRES 5-13-2013

ASSIGNEE hereby acknowledges receipt of the entire right, title and interest in and to the PATENT RIGHTS.

INO THERAPEAUTICS LLC

By William B. Schmiller

Title Assistant Secretary

Date August 20, 2012

Daria Cooney

DARIA COONEY
NOTARY PUBLIC
WARREN COUNTY, NJ.
MY COMMISION EXPIRES 5-13-2013

SCHEDULE A: PATENT APPLICATIONS

U.S. Application No. 12/820,866

U.S. Application No. 12/821,020

U.S. Application No. 12/821,041

22897359.doc

Electronic Patent Application Fee Transmittal	
Application Number:	
Filing Date:	
Title of Invention:	METHODS FOR TREATING PATIENTS WHO ARE CANDIDATES FOR INHALED NITRIC OXIDE TREATMENT
First Named Inventor/Applicant Name:	James S. Baldassarre
Filer:	Janis K. Fraser/Nancy Bechet
Attorney Docket Number:	26047-0003008
Filed as Large 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 application filing	1011	1	390	390
Utility Search Fee	1111	1	620	620
Utility Examination Fee	1311	1	250	250
Request for Prioritized Examination	1817	1	4800	4800
Pages:				
Claims:				
Claims in excess of 20	1202	10	62	620
Miscellaneous-Filing:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Publ. Fee- early, voluntary, or normal	1504	1	300	300
Processing Fee, except for Provis. apps	1808	1	130	130
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Miscellaneous:				
		Total in USD ($)		**7110**

Electronic Acknowledgement Receipt	
EFS ID:	14289781
Application Number:	13683417
International Application Number:	
Confirmation Number:	1654
Title of Invention:	METHODS FOR TREATING PATIENTS WHO ARE CANDIDATES FOR INHALED NITRIC OXIDE TREATMENT
First Named Inventor/Applicant Name:	James S. Baldassarre
Customer Number:	94169
Filer:	Janis K. Fraser/Paul Stovenour
Filer Authorized By:	Janis K. Fraser
Attorney Docket Number:	26047-0003008
Receipt Date:	21-NOV-2012
Filing Date:	
Time Stamp:	14:51:21
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$7110
RAM confirmation Number	3100
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	TrackOne Request	request26047_0003008.pdf	139111 1349058d129ebeffae69e43bebaca5167d07941b	no	1
Warnings:					
Information:					
2	Application Data Sheet	ADS26047_0003008.pdf	1396088 96c7a194bfaea9c15257e17a27100606fe8b1228	no	6
Warnings:					
Information:					
3	Transmittal of New Application	paptrans26047_0003008.pdf	94633 a00148b919f1d2aeeccbde1c787f8f83e4b77f08	no	2
Warnings:					
Information:					
4		application26047_0003008.pdf	237857 12cfc32fc5ce6b5e95d62a34e7e81e04525796a0	yes	29

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Specification	1	22
	Claims	23	28
	Abstract	29	29

Warnings:					
Information:					
5	Oath or Declaration filed	declaration26047_0003008.pdf	121206 03333a56dea21196bc473a0d94190e1c8f38ed18	no	3
Warnings:					
Information:					
6	Power of Attorney	power003008.pdf	4308097 ed0c2c24e3139f4fa49dbe86a4ce3dd14a39ec8d	no	86
Warnings:					
Information:					
7	Fee Worksheet (SB06)	fee-info.pdf	41873 d234124806f627f7d200a88e18317ddef646f535	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	6338865		

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.

CERTIFICATION AND REQUEST FOR PRIORITIZED EXAMINATION UNDER 37 CFR 1.102(e) (Page 1 of 1)

First Named Inventor:	James S. Baldassarre	Nonprovisional Application Number (if known):	
Title of Invention:	METHODS FOR TREATING PATIENTS WHO ARE CANDIDATES FOR INHALED NITRIC OXIDE TREATMENT		

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), 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, examination fee, and any required excess claims and application size fees are filed with the request or have been already been paid.

2. The application contains or is amended to contain no more than four independent claims and no more than thirty total claims, and no 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 nonprovisional 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 nonprovisional 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 oath or declaration under 37 CFR 1.63 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 nonprovisional 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 November 21, 2012
Name Janis K. Fraser, Ph.D., J.D. (Print/Typed)	Practitioner Registration Number 34,819

Note: *Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required in accordance with 37 CFR 1.33 and 11.18. Please see 37 CFR 1.4(d) for the form of the signature. If necessary, submit multiple forms for more than one signature, see below*.*

☒ *Total of 1 forms are submitted.

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PTO/AIA/14 (08-12)
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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	26047-0003008
	Application Number	
Title of Invention	METHODS FOR TREATING PATIENTS WHO ARE CANDIDATES FOR INHALED NITRIC OXIDE TREATMENT	

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	US

Mailing Address of Inventor:

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

Inventor 2 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Ralf		Rosskamp	

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

City	Chester	State/Province	NJ	Country of Residence	US

Mailing Address of Inventor:

Address 1	1 Byron Court		
Address 2			
City	Chester	State/Province	NJ
Postal Code	07930	Country	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).

PTO/AIA/14 (08-12)
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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	26047-0003008
	Application Number	
Title of Invention	METHODS FOR TREATING PATIENTS WHO ARE CANDIDATES FOR INHALED NITRIC OXIDE TREATMENT	

☐ **An Address is being provided for the correspondence Information of this application.**			
Customer Number	94169		
Email Address		Add Email	Remove Email

Application Information:

Title of the Invention	METHODS FOR TREATING PATIENTS WHO ARE CANDIDATES FOR INHALED NITRIC OXIDE TREATMENT		
Attorney Docket Number	26047-0003008	**Small Entity Status Claimed**	☐
Application Type	Nonprovisional		
Subject Matter	Utility		
Suggested Class (if any)		**Sub Class (if any)**	
Suggested Technology Center (if any)			
Total Number of Drawing Sheets (if any)		**Suggested Figure for Publication (if any)**	

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.

Prior Application Status	Pending		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
	Continuation of	12820866	2010-06-22

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	26047-0003008
	Application Number	
Title of Invention	METHODS FOR TREATING PATIENTS WHO ARE CANDIDATES FOR INHALED NITRIC OXIDE TREATMENT	

Prior Application Status	Abandoned		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
12820866	Continuation of	12494598	2009-06-30
Prior Application Status	Pending		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
	Continuation of	13651660	2012-10-15
Prior Application Status	Patented		Remove

Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
13651660	Continuation of	12821041	2010-06-22	8293284	2012-10-23

Prior Application Status	Abandoned		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
12821041	Continuation of	12494598	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 benefit of foreign priority and to identify any prior foreign application for which priority is not claimed. 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(a).

Remove

Application Number	Country i	Filing Date (YYYY-MM-DD)	Priority Claimed
			◯ Yes ◯ No

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

Authorization to Permit Access:

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

PTO/AIA/14 (08-12)
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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	26047-0003008
	Application Number	
Title of Invention	METHODS FOR TREATING PATIENTS WHO ARE CANDIDATES FOR INHALED NITRIC OXIDE TREATMENT	

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.

Applicant 1

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.

Remove

◉	Assignee	○	Legal Representative under 35 U.S.C. 117
○	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 Assignee is an Organization check here. ☒

Organization Name	INO Therapeutics LLC		
Mailing Address Information:			
Address 1	Perryville III Corporate Park		
Address 2	53 Frontage Road, 3rd Floor		
City	Hampton	**State/Province**	NJ
Country [i]	US	Postal Code	08827-9001
Phone Number		Fax Number	

PTO/AIA/14 (08-12)
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	26047-0003008
	Application Number	
Title of Invention	METHODS FOR TREATING PATIENTS WHO ARE CANDIDATES FOR INHALED NITRIC OXIDE TREATMENT	

Email Address	

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

Signature:

Remove

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

Signature	/Janis Fraser/			Date (YYYY-MM-DD)	2012-11-21
First Name	Janis	Last Name	Fraser	Registration Number	34819

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

This collection of information is required by 37 CFR 1.76. 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 23 minutes to complete, including gathering, preparing, and submitting the completed application data sheet form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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

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 records.

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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.

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.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	: James S. Baldassarre et al.	Art Unit	: Unknown
Serial No.	: N/A	Examiner	: Unknown
Filed	: Herewith		
Title	: METHODS FOR TREATING PATIENTS WHO ARE CANDIDATES FOR INHALED NITRIC OXIDE TREATMENT		

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

SUBMISSION OF DECLARATIONS

The attached declarations of co-inventors James S. Baldassarre and Ralf Rosskamp are copies of the declarations originally filed in the parent application, U.S. serial no. 13/651,660. The present application is a continuation of U.S. serial no. 13/651,660.

Respectfully submitted,

Date: November 21, 2012

/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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I hereby certify under 37 CFR §1.8(a) that this correspondence is either (A) addressed as set out in 37 CFR §1.1(a) and being deposited with the United States Postal Service as first class mail with sufficient postage, or (B) being transmitted by facsimile in accordance with 37 CFR § 1.6(d) or via the Office electronic filing system in accordance with 37 CFR § 1.6(a)(4), on the date indicated below.

November 21, 2012
Date of Deposit or Transmission

/Nancy Bechet/
Signature

Nancy Bechet
Typed or Printed Name of Person Signing Certificate

Attorney Docket No. 26047-0003007

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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: Ralf Rosskamp Date (Optional): Oct 8, 2012

Signature: R. Ray Mueller

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.

Attorney Docket No. 28047-0003007

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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.

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

INFORMATION DISCLOSURE STATEMENT BY APPLICANT
(Not for submission under 37 CFR 1.99)

Application Number	13683417
Filing Date	2012-11-21
First Named Inventor	Baldassarre
Art Unit	
Examiner Name	
Attorney Docket Number	26047-0003008

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	5873359		1999-02-23	Zapol et al.	
	2	6063407		2000-05-16	Zapol et al.	
	3	6601580		2003-08-05	Bloch et al.	
	4	7557087		2009-07-07	Rothbard et al.	

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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	20040106954		2004-06-03	Whitehurst et al.	
	2	20090018136		2009-01-15	Oppenheimer et al.	

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	13683417
	Filing Date	2012-11-21
	First Named Inventor	Baldassarre
	Art Unit	
	Examiner Name	
	Attorney Docket Number	26047-0003008

	3	20090029371		2009-01-29	Elliot	
	4	20090149541		2009-06-11	Stark et al.	
	5	20090176772		2009-07-09	Blackburn et al.	

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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	EP1682672	EP		2006-07-26			☐
	2	WO2005004884	WO		2005-01-20			☐
	3	WO2006127907	WO		2006-11-30			☐
	4	WO2010019540	WO		2010-02-18			☐

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

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	13683417
	Filing Date	2012-11-21
	First Named Inventor	Baldassarre
	Art Unit	
	Examiner Name	
	Attorney Docket Number	26047-0003008

	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)	☐
	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	☐

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	13683417
	Filing Date	2012-11-21
	First Named Inventor	Baldassarre
	Art Unit	
	Examiner Name	
	Attorney Docket Number	26047-0003008

	12	Barst et al., "Vasodilator Testing with Nitric Oxide and/or Oxygen in Pediatric Pulmonary Hypertension," Pediatric Cardiology; Published online 20 April 2010, 9 pages	☐
	13	Beggs et al., "Cardiac Failure in Children," 17th Expert Committee on the Selection and Use of Essential Medicines, Geneva, March 2009, 31 pages	☐
	14	Beghetti et al., "Inhaled nitric oxide can cause severe systemic hypotension," Journal of Pediatrics, page 844 (1997)	☐
	15	Beghetti et al., "Inhaled nitric oxide and congenital cardiac disease," Cardiol. Young, Vol. 11, pages 142-152 (2001)	☐
	16	Behera et al., "Nesiritide Improves Hemodynamics in Children with Dilated Cardiomyopathy: A Pilot Study," Pediatr. Cardiol., Vol. 30, pages 26-34 (2009)	☐
	17	Bhagavan et al., "Potential role of ubiquinone (coenzyme Q10) in pediatric cardiomyopathy," Clinical Nutrition, Vol. 24, pages 331-338 (2005)	☐
	18	Bichel et al., "Successful weaning from cardiopulmonary bypass after cardiac surgery using inhaled nitric oxide", Pediatric Anaesthesia, Vol. 7, pages 335-339 (1997)	☐
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Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

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Application Number:	13683417
International Application Number:	
Confirmation Number:	1654
Title of Invention:	METHODS FOR TREATING PATIENTS WHO ARE CANDIDATES FOR INHALED NITRIC OXIDE TREATMENT
First Named Inventor/Applicant Name:	James S. Baldassarre
Customer Number:	94169
Filer:	Janis K. Fraser/Nancy Bechet
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Attorney Docket Number:	26047-0003008
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Applicant	: James S. Baldassarre et al.	Art Unit	: Unknown
Serial No.	: 13/683,417	Examiner	: Unknown
Filed	: November 21, 2012	Conf. No.	: 1654
Title	: METHODS FOR TREATING PATIENTS WHO ARE CANDIDATES FOR INHALED NITRIC OXIDE TREATMENT		

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Respectfully submitted,

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	40	INOmax (nitric oxide) for inhalation 100 and 800 ppm (parts per million), drug label insert, 2007, 2 pages	☐
	41	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)	☐
	42	James et al., "Treatment of heart failure in children," Current Pediatrics, Vol. 15, 539-548 (2005)	☐
	43	JP 2009157623 Office Action dated 02/15/2011, 3 pages	☐
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	Application Number	13683417
	Filing Date	2012-11-21
	First Named Inventor	Baldassarre
	Art Unit	
	Examiner Name	
	Attorney Docket Number	26047-0003008

	45	JP 2009157623 Office Action dated 07/30/2010, 6 pages	☐
	46	JP 2009157623 Office Action response filed 06/18/2010, 37 pages (no translation)	☐
	47	JP 2009157623 request for accelerated exam filed 01/15/2010 (60 pages)	☐
	48	JP 2009157623 response filed 11/30/2010, 58 pages	☐
	49	Kay et al., "Congestive heart failure in pediatric patients," From the Department of Pediatrics, Duke University Medical Center, by Mosby, Inc., 6 pages (2001)	☐
	50	Kazerooni et al., "Cardiopulmonary Imaging," Lippincott Williams & Wilkins, pages 234-235 (2 pages) (2004)	☐

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Signature	/Janis K. Fraser/	Date (YYYY-MM-DD)	2012-12-03
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EFS ID:	14368377
Application Number:	13683417
International Application Number:	
Confirmation Number:	1654
Title of Invention:	METHODS FOR TREATING PATIENTS WHO ARE CANDIDATES FOR INHALED NITRIC OXIDE TREATMENT
First Named Inventor/Applicant Name:	James S. Baldassarre
Customer Number:	94169
Filer:	Janis K. Fraser/Nancy Bechet
Filer Authorized By:	Janis K. Fraser
Attorney Docket Number:	26047-0003008
Receipt Date:	03-DEC-2012
Filing Date:	
Time Stamp:	15:48:16
Application Type:	Utility under 35 USC 111(a)

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1	Transmittal Letter	IDSnumbertwo_26047_0003008.pdf	63704 2d081346f9dfeb15144cd8c986c82062eb4955ba	no	1
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	: James S. Baldassarre et al.	Art Unit	: Unknown
Serial No.	: 13/683,417	Examiner	: Unknown
Filed	: November 21, 2012	Conf. No.	: 1654
Title	: METHODS FOR TREATING PATIENTS WHO ARE CANDIDATES FOR INHALED NITRIC OXIDE TREATMENT		

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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: December 3, 2012

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

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	Application Number	13683417
	Filing Date	2012-11-21
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	1	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)	☐
	2	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)	☐
	3	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)	☐
	4	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)	☐
	5	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)	☐
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	7	Lavigne et al., "Cardiovascular Outcomes of Pediatric Seroreverters Perinatally Exposed to HAART," Cardiovascular Toxicology, Vol. 4, pages 187-197 (2004)	☐
	8	Letter of Acceptance for AU 2010202422, dated 10/7/2010	☐
	9	Letter of acceptance of AU application 2009202685, dated 08/10/2010, 3 pages	☐
	10	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)	☐
	11	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>>"	☐

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	12	Lipshultz, "Ventricular dysfunction clinical research in infants, children and adolescents," Progress in Pediatric Cardiology, Vol. 12, pages 1-28 (2000)	☐
	13	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)	☐
	14	Lipshultz, "Clinical research directions in pediatric cardiology," Current Opinion in Pediatrics, Vol. 21, pages 585-593 (2009)	☐
	15	Lipshultz, "Establishing norms for echocardiographic measurement of cardiovascular structures and function in children," J. Appl. Physiol., Vol. 99, pages 386-388 (2005)	☐
	16	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)	☐
	17	Lipshultz et al., "Cardiovascular Trials in Long-Term Survivors of Childhood Cancer," Journal of Clinical Oncology, Vol. 22, Number 5, pages 769-773 (2004)	☐
	18	Lipshultz et al., "Long-Term Enalapril Therapy for Left Ventricular Dysfunction in Doxorubicin-Treated Survivors of Childhood Cancer," Journal of Clinical Oncology, Vol. 20, No 23, pages 4517-4522 (2002)	☐
	19	Lipshultz, "Frequency of clinically unsuspected myocardial injury at a children's hospital," American Heart Journal, Vol. 151, No 4, pages 916-922 (2006)	☐
	20	Loh et al., "Cardiovascular Effects of Inhaled Nitric Oxide in Patients with Left Ventricular Dsyfunction," Circulation, Vol. 90, pages 2780-2785 (1994)	☐
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	22	Madriago et al., "Heart Failure in Infants and Children," Pediatrics in Review, Vol. 31, pages 4-12 (2010)	☐

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	23	Magee et al., "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," 10/1/2004-10/31/2006, Research project description, 1 page, http://www.rbht.nhs.uk/research	☐
	24	Malloy, "Nitric Oxide Weaning, RT: For Decision Makers in Respiratory Care," http://rtmagazine.com/issues/articles/2000-12_05.asp, 3 pages, December 2000	☐
	25	Martinez et al., "Dermatological Cryosurgery in Primary Care with Dimethyl Ether Propane Spray in Comparison with Liquid Nitrogen," Atnecion Primaria, Vol. 18, No. 5, pages 211 and 216 (1996)	☐
	26	Matsumoto et al., "Effect of Inhaled Nitric Oxide on Gas Exchange in Patients with Congestive Heart Failure," Annals of Internal Medicine, Vol. 130, No. 1, pages 40-44 (1999)	☐
	27	Meyler's Side Effects of Drugs: The International Encyclopedia of Adverse Drug Reactions and Interactions, Nitric Oxide, Fifteenth Edition, Elsevier B.V. (2006)	☐
	28	Michelakis et al., "Oral Sildenafil Is an Effective and Specific Pulmonary Vasodilator in Patients with Pulmonary Arterial Hypertension: Comparison with Inhaled Nitric Oxide," Circulation Vol. 105, pages 2398-2403 (2002)	☐
	29	Miller et al., "Nutrition in Pediatric Cardiomyopathy," Prog. Pediatr. Cardiol. Vol. 24(1), pages 59-71 (2007)	☐
	30	Mone, "Effects of Environmental Exposures on the Cardiovascular System: Prenatal Period Through Adolescence," Pediatrics. Vol. 113, No 4, pages 1058-1069 (2004)	☐
	31	Morales-Blanhir et al., "Clinical value of vasodilator test with inhaled nitric oxide for predicting long-term response to oral vasodilators in pulmonary hypertension," Respiratory Medicine, Vol. 98, pages 225-234 (2004)	☐
	32	Moss et al., "Moss and Adams' Heart Disease in Infants, Children, and Adolescents," Coarctation of the Aorta, Vol. 1, page 991 in part (2007)	☐
	33	Murray, "Angiotensin Converting Enzyme Inhibitory Peptides Derived from Food Proteins: Biochemistry, Bioactivity and Production," Current Pharmaceutical Design, pages 773-791 (2007)	☐

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	34	Murray et al., "Nitric Oxide and Septic Vascular Dysfunction," Anesth. Analg. Vol. 90, pages 89-101 (2000)	☐
	35	Natori et al., "Inhaled Nitric Oxide Modifies Left Ventricular Diastolic Stress in the Presence of Vasoactive Agents in Heart Failure," Am. J. Respir. Crit. Care Med, Vol. 167, pages 895-901 (2003)	☐
	36	NIH CC: Critical Care Services, http://www.cc.nih.gov/ccmd/clinical_services.html; retrieved 3/10/2011, 3 pages	☐
	37	"NIH Clinical Center 2 Critical Care Medicine Department Sample Rotations, Updated January 2007 <<http://www.cc.nih.gov/ccmd/prof_opps/rotation.html>>"	☐
	38	NIH Clinical Center Services, retrieved at <http://www.cc.nih.gov/ccmd/clinical_services.html>> on 08/18/2010	☐
	39	NIH Clinical Center, Department Policy and Procedure Manual for the Critical Care Therapy and Respiratory Care Section; Nitric Oxide Therapy, sections 3.1-3.1.2 & 5.2.3 (2000)	☐
	40	NIH Clinical Center 2 Critical Care Medicine Department Sample Rotations, Updated January 2007	☐
	41	Notification of Reason for Rejection, mailed 7/30/2010, from Japanese Patent Application No. 2009-157623 (cites foreign references)	☐
	42	Office Action for AU 2010202422 dated 07/09/2010, 3 pages	☐
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	45	Office Action Response for AU 2009202685 to 03/15/2010 OA, filed 06/08/2010 (16 pages)	☐
	46	Office Action Response for JP2007157623 filed on 11/12/2009 (no English translation)	☐
	47	Office Action Response to AU 2010202422 OA dated 07/09/2010, response filed 09/01/2010	☐
	48	www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidance/ucm073087.pdf, March 1995	☐

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Signature	/Janis K. Fraser/	Date (YYYY-MM-DD)	2012-12-04
Name/Print	Janis K. Fraser	Registration Number	34819

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Electronic Acknowledgement Receipt	
EFS ID:	14380268
Application Number:	13683417
International Application Number:	
Confirmation Number:	1654
Title of Invention:	METHODS FOR TREATING PATIENTS WHO ARE CANDIDATES FOR INHALED NITRIC OXIDE TREATMENT
First Named Inventor/Applicant Name:	James S. Baldassarre
Customer Number:	94169
Filer:	Janis K. Fraser/Nancy Bechet
Filer Authorized By:	Janis K. Fraser
Attorney Docket Number:	26047-0003008
Receipt Date:	04-DEC-2012
Filing Date:	
Time Stamp:	15:50:19
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	IDSTHREE0003008.pdf	63681 c48e61f534a02b72a8471a430f76dde8f5488275	no	1

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	: James S. Baldassarre et al.	Art Unit	: Unknown
Serial No.	: 13/683,417	Examiner	: Unknown
Filed	: November 21, 2012	Conf. No.	: 1654
Title	: METHODS FOR TREATING PATIENTS WHO ARE CANDIDATES FOR INHALED NITRIC OXIDE TREATMENT		

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Please consider the references listed on the enclosed SB-08 form. Under 35 USC §120, this application relies on the earlier filing date of application serial number 12/821,041. The listed references were submitted or otherwise made of record in application serial no. 12/821,041, so are not provided with this filing.

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: December 4, 2012

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

Customer Number 94169
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99)**		
	Application Number	13683417
	Filing Date	2012-11-21
	First Named Inventor	Baldassarre
	Art Unit	
	Examiner Name	
	Attorney Docket Number	26047-0003008

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	1	Ovodov et al., "Nitric Oxide: Clinical Applications," Seminars in Anesthesia, Saunders, CO, New York,, NY, Vol 19, No. 2, pages 88-97 (2000)	☐
	2	Pazopanib Plus Lapatinib Compared to Lapatinib Alone in Subjects With Inflammatory Breast Cancer, page 4, ClinicalTrials.gov, <<http://clinicaltrials.gov/ct2/show/NCT00558103>> April 22, 2010	☐
	3	PCT/US2010/038652 Search Report dated 07/29/2010, 16 pages	☐
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	8	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)	☐
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	11	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)	☐

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	12	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)	☐
	13	Search Report from EP 09251949 dated 05/10/10	☐
	14	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)	☐
	15	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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	23	Steinhorn, "Persistent Pulmonary Hypertension in the Newborn and Infant," Vol. 1(2), pages 287-299 (1987) [downloadedfrom www. Emedicine.com on June 10, 2008	☐
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	27	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", InterenetJournal 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>>	☐
	28	The American Illustrated Medical Dictionary (Dorland, 7th ed., page 113) (1914)	☐
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	33	Towbin et al., "Incidence, Causes, and Outcomes of Dilated Cardiomyopathy in Children," JAMA, Vol. 296, No. 15, pages 1867-1876 (2006)	☐

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	Filing Date	2012-11-21
	First Named Inventor	Baldassarre
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	38	"Use of Inhaled Nitric Oxide," American Academy of Pediatrics - Committee on Fetus and Newborn, Pediatrics Vol. 106, No. 2, pages 344-345 (2000)	☐
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	40	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)	☐
	41	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)	☐
	42	Weinberger et al., "The Toxicology of Inhaled Nitric Oxide," Toxicological Sciences, Vol. 59, pages 5-16 (2001)	☐
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	44	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)	☐

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	45	Wessel et al., "Managing low cardiac output syndrome after congenital heart surgery," Crit. Care Med., Vol. 29(10) pages S220-S230 (2001)	☐
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	First Named Inventor	Baldassarre
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Name/Print	Janis K. Fraser	Registration Number	34819

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EFS ID:	14388842
Application Number:	13683417
International Application Number:	
Confirmation Number:	1654
Title of Invention:	METHODS FOR TREATING PATIENTS WHO ARE CANDIDATES FOR INHALED NITRIC OXIDE TREATMENT
First Named Inventor/Applicant Name:	James S. Baldassarre
Customer Number:	94169
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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.

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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.

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	: James S. Baldassarre et al.	Art Unit	: Unknown
Serial No.	: 13/683,417	Examiner	: Unknown
Filed	: November 21, 2012	Conf. No.	: 1654
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

FOURTH INFORMATION DISCLOSURE STATEMENT

Please consider the references listed on the enclosed SB-08 form. Under 35 USC §120, this application rlies on the earlier filing date of application serial number 12/821,041. The listed references were submitted or otherwise made of record in application serial no. 12/821,041, so are not provided with this filing.

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: December 5, 2012

/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	13683417
	Filing Date	2012-11-21
	First Named Inventor	Baldassarre
	Art Unit	
	Examiner Name	
	Attorney Docket Number	26047-0003008

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	13683417
	Filing Date	2012-11-21
	First Named Inventor	Baldassarre
	Art Unit	
	Examiner Name	
	Attorney Docket Number	26047-0003008

	1	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	☐
	2	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)	☐
	3	Barrington et al., "Inhaled nitric oxide for respiratory failure in preterm infants (review)," The Cochrane Collaboration, Wiley Publishers, 3 pages (2009)	☐
	4	Barst, Pediatr., "Vasodilator Testing with Nitric Oxide and/or Oxygen in Pediatric Pulmonary Hypertension," Cardiol., Vol. 31, pages 598-606 (2010)	☐
	5	Macrae, "Drug therapy in persistent pulmonary hypertension of the newborn," Semin. Neonatal, Vol. 2, pages 49-58 (1997)	☐
	6	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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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	13683417
	Filing Date	2012-11-21
	First Named Inventor	Baldassarre
	Art Unit	
	Examiner Name	
	Attorney Docket Number	26047-0003008

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)	2012-12-06
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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EFS ID:	14400319
Application Number:	13683417
International Application Number:	
Confirmation Number:	1654
Title of Invention:	METHODS FOR TREATING PATIENTS WHO ARE CANDIDATES FOR INHALED NITRIC OXIDE TREATMENT
First Named Inventor/Applicant Name:	James S. Baldassarre
Customer Number:	94169
Filer:	Janis K. Fraser/Nancy Bechet
Filer Authorized By:	Janis K. Fraser
Attorney Docket Number:	26047-0003008
Receipt Date:	06-DEC-2012
Filing Date:	
Time Stamp:	14:01:22
Application Type:	Utility under 35 USC 111(a)

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1	Transmittal Letter	FIFTHIDS0003008.pdf	63672 fbc2cf3c4fe18efbebe6d73f4f6e311cdb5141d	no	1
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	: James S. Baldassarre et al.	Art Unit	: Unknown
Serial No.	: 13/683,417	Examiner	: Unknown
Filed	: November 21, 2012	Conf. No.	: 1654
Title	: METHODS FOR TREATING PATIENTS WHO ARE CANDIDATES FOR INHALED NITRIC OXIDE TREATMENT		

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Alexandria, VA 22313-1450

FIFTH INFORMATION DISCLOSURE STATEMENT

Please consider the references listed on the enclosed SB-08 form. Under 35 USC §120, this application relies on the earlier filing date of application serial number 12/821,041. The listed references were submitted or otherwise made of record in application serial no. 12/821,041, so are not provided with this filing.

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: December 6, 2012

/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
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99)**		
	Application Number	13683417
	Filing Date	2012-11-21
	First Named Inventor	Baldassarre
	Art Unit	
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	Attorney Docket Number	26047-0003008

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	13683417
	Filing Date	2012-11-21
	First Named Inventor	Baldassarre
	Art Unit	
	Examiner Name	
	Attorney Docket Number	26047-0003008

	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 Amendment (Accelerated Exam-Transmittal Amendment/Reply) in U.S. Serial No. 12/820,866 mailed September 23, 2010, 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 Amendment (Accelerated Exam-Transmittal Amendment/Reply) in U.S. Serial No. 12/820,866 mailed November 2, 2010, 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 (Accelerated Exam-Transmittal Amendment/Reply) in U.S. Serial No. 12/820,866 mailed September 23, 2010, filed March 1, 2011 (9 pages)	☐
	9	Lee & Hayes, Reply After Final (Accelerated Exam-Transmittal Amendment/Reply) in U.S. Serial No. 12/820,866 mailed September 23, 2010, filed March 1, 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 (Accelerated Exam-Transmittal Amendment/Reply) in U.S. Serial No. 12/820,866 mailed November 2, 2010, filed May 2, 2011 (9 pages)	☐

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	Application Number	13683417
	Filing Date	2012-11-21
	First Named Inventor	Baldassarre
	Art Unit	
	Examiner Name	
	Attorney Docket Number	26047-0003008

	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)	☐
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	22	Lee & Hayes, Reply after Final (Accelerated Exam-Transmittal Reply) in U.S. Serial No. 12/820,980, mailed November 2, 2010, filed May 2, 2011 (23 pages)	☐

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	Attorney Docket Number	26047-0003008

	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, mailed June 10, 2011, 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)	☐
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	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, mailed August 13, 2010, 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, mailed June 27, 2011, 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)	☐
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	Attorney Docket Number	26047-0003008

	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 Reply, in U.S. Serial No. 12/821,020, mailed June 15, 2012, 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 Amendment in U.S. Serial No. 12/821,041, mailed August 17, 2010, filed February 14, 2011 (28 pages)	☐
	40	Lee & Hayes, Supplemental Reply Amendment in U.S. Serial No. 12/821,041, mailed August 17, 2010, 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, mailed June 27, 2011, 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., in U.S. Serial No. 12/821,041, Supplemental Amendment and Remarks, filed May 11, 2012 (32 pages)	☐

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	13683417
	Filing Date	2012-11-21
	First Named Inventor	Baldassarre
	Art Unit	
	Examiner Name	
	Attorney Docket Number	26047-0003008

	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, mailed June 19, 2012, filed August 15, 2012 (17 pages)	☐
	47	Lee & Hayes Amendment in Reply to Office Action in U.S. Serial No. 12/820,866, mailed June 8, 2011, 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)	☐

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.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	13683417
	Filing Date	2012-11-21
	First Named Inventor	Baldassarre
	Art Unit	
	Examiner Name	
	Attorney Docket Number	26047-0003008

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)	2012-12-07
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:	14410799
Application Number:	13683417
International Application Number:	
Confirmation Number:	1654
Title of Invention:	METHODS FOR TREATING PATIENTS WHO ARE CANDIDATES FOR INHALED NITRIC OXIDE TREATMENT
First Named Inventor/Applicant Name:	James S. Baldassarre
Customer Number:	94169
Filer:	Janis K. Fraser/Nancy Bechet
Filer Authorized By:	Janis K. Fraser
Attorney Docket Number:	26047-0003008
Receipt Date:	07-DEC-2012
Filing Date:	
Time Stamp:	13:07:22
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	IDSSIXTH0003008.pdf	63650 b7b09fd7b2aba0a7b5e812752ef7fcaa794cc29b	no	1
Warnings:					
Information:					

2	Information Disclosure Statement (IDS) Form (SB08)	SB08Sixth0003008.pdf	613500 4d485e099668776476a2c55bdc582ea0f8076e96	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):	677150

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

Applicant	: James S. Baldassarre et al.	Art Unit	: Unknown
Serial No.	: 13/683,417	Examiner	: Unknown
Filed	: November 21, 2012	Conf. No.	: 1654
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

SIXTH INFORMATION DISCLOSURE STATEMENT

Please consider the references listed on the enclosed SB-08 form. Under 35 USC §120, this application relies on the earlier filing date of application serial number 13/651,660. The listed references were submitted or otherwise made of record in application serial no. 13/651,660, so are not provided with this filing.

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: December 7, 2012

/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

22948229.doc

CERTIFICATE OF (A) MAILING BY FIRST CLASS MAIL OR (B) TRANSMISSION
I hereby certify under 37 CFR §1.8(a) that this correspondence is either (A) addressed as set out in 37 CFR §1.1(a) and being deposited with the United States Postal Service as first class mail with sufficient postage, or (B) being transmitted by facsimile in accordance with 37 CFR § 1.6(d) or via the Office electronic filing system in accordance with 37 CFR § 1.6(a)(4), on the date indicated below.

December 7, 2012
Date of Deposit or Transmission

/Nancy Bechet/
Signature

Nancy Bechet
Typed or Printed Name of Person Signing Certificate

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	13683417
	Filing Date	2012-11-21
	First Named Inventor	Baldassarre
	Art Unit	
	Examiner Name	
	Attorney Docket Number	26047-0003008

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
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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]
	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	13683417
	Filing Date	2012-11-21
	First Named Inventor	Baldassarre
	Art Unit	
	Examiner Name	
	Attorney Docket Number	26047-0003008

	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)	☐

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.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	13683417
	Filing Date	2012-11-21
	First Named Inventor	Baldassarre
	Art Unit	
	Examiner Name	
	Attorney Docket Number	26047-0003008

CERTIFICATION STATEMENT

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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)	2012-12-10
Name/Print	Janis K. Fraser	Registration Number	34819

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

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

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

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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:	14423851
Application Number:	13683417
International Application Number:	
Confirmation Number:	1654
Title of Invention:	METHODS FOR TREATING PATIENTS WHO ARE CANDIDATES FOR INHALED NITRIC OXIDE TREATMENT
First Named Inventor/Applicant Name:	James S. Baldassarre
Customer Number:	94169
Filer:	Janis K. Fraser/Nancy Bechet
Filer Authorized By:	Janis K. Fraser
Attorney Docket Number:	26047-0003008
Receipt Date:	10-DEC-2012
Filing Date:	
Time Stamp:	14:12:49
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	IDSSeventh0003008.pdf	64913 b8752c865219e540aa3f1b257f891773054a d38b	no	2

Warnings:
Information:

2	Information Disclosure Statement (IDS) Form (SB08)	SB08Numberseven260470003008.pdf	612448 4559b63a68af6156e7e2e9d48dc581cee3b05d3c	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.					
3	Non Patent Literature	Expressaban0003002.pdf	67912 b0e52440aaca4ec950a8cc425d939f15fc630ab5	no	1
Warnings:					
Information:					
		Total Files Size (in bytes):	745273		

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

Applicant	: James S. Baldassarre et al.	Art Unit	: Unknown
Serial No.	: 13/683,417	Examiner	: Unknown
Filed	: November 21, 2012	Conf. No.	: 1654
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

SEVENTH INFORMATION DISCLOSURE STATEMENT

Please consider the documents listed on the enclosed SB-08 form. Under 35 USC §120, this application relies on the earlier filing date of application serial number 13/651,660. Documents numbered 1-4 were submitted in application serial no. 13/651,660, so are not provided with this filing. Document number 5 is enclosed.

The following related U.S. applications are brought to the Examiner's attention:

12/494,598 filed June 30, 2009 (abandoned)
12/820,866 filed June 22, 2010 (abandoned)
12/820,980 filed June 22, 2010 (abandoned)
12/821,020 filed June 22, 2010 (issued as U.S. patent no. 8,282,966)
12/821,041 filed June 22, 2010 (issued as U.S. patent no. 8,293,284)
13/651,660 filed October 15, 2012 (pending)
13/683,236 filed November 21, 2012 (pending)
13/683,444 filed November 21, 2012 (pending)

CERTIFICATE OF (A) MAILING BY FIRST CLASS MAIL OR (B) TRANSMISSION
I hereby certify under 37 CFR §1.8(a) that this correspondence is either (A) addressed as set out in 37 CFR §1.1(a) and being deposited with the United States Postal Service as first class mail with sufficient postage, or (B) being transmitted by facsimile in accordance with 37 CFR § 1.6(d) or via the Office electronic filing system in accordance with 37 CFR § 1.6(a)(4), on the date indicated below.

December 10, 2012
Date of Deposit or Transmission

/Nancy Bechet/
Signature

Nancy Bechet
Typed or Printed Name of Person Signing Certificate

This statement is being filed within three months of the present application's filing date and before the receipt of a first Office Action on the merits. Apply any necessary charges or credits to Deposit Account 06-1050, referencing the above attorney docket number.

Respectfully submitted,

Date: December 10, 2012

/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

22948231.doc

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number: 13/683,417

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			N/A	390
SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	620
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	250
TOTAL CLAIMS (37 CFR 1.16(i))	30 minus 20 =	* 10			OR	x 62 =	620
INDEPENDENT CLAIMS (37 CFR 1.16(h))	3 minus 3 =	*				x 250 =	0.00
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			TOTAL	1880

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	RATE($)	ADDITIONAL FEE($)		RATE($)	ADDITIONAL FEE($)
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
13/683,417	11/21/2012	3771	2180	26047-0003008	30	3

CONFIRMATION NO. 1654

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

FILING RECEIPT

OC000000058174400

Date Mailed: 12/20/2012

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;
Ralf Rosskamp, Chester, NJ;

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 12/820,866 06/22/2010 ABN
which is a CON of 12/494,598 06/30/2009 ABN
This application 13/683,417
is a CON of 13/651,660 10/15/2012
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: 12/14/2012
The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 13/683,417**

Projected Publication Date: 03/28/2013

Non-Publication Request: No

Early Publication Request: No

Title

METHODS FOR TREATING PATIENTS WHO ARE CANDIDATES FOR INHALED NITRIC OXIDE TREATMENT

Preliminary Class

128

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.

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at http://www.uspto.gov/web/offices/pac/doc/general/index.html.

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 (1-866-999-4158).

LICENSE FOR FOREIGN FILING UNDER

Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

GRANTED

The applicant has been granted a license under 35 U.S.C. 184, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" followed by a date appears on this form. Such licenses are issued in all applications where the conditions for issuance of a license have been met, regardless of whether or not a license may be required as set forth in 37 CFR 5.15. The scope and limitations of this license are set forth in 37 CFR 5.15(a) unless an earlier license has been issued under 37 CFR 5.15(b). The license is subject to revocation upon written notification. The date indicated is the effective date of the license, unless an earlier license of similar scope has been granted under 37 CFR 5.13 or 5.14.

This license is to be retained by the licensee and may be used at any time on or after the effective date thereof unless it is revoked. This license is automatically transferred to any related applications(s) filed under 37 CFR 1.53(d). This license is not retroactive.

The grant of a license does not in any way lessen the responsibility of a licensee for the security of the subject matter as imposed by any Government contract or the provisions of existing laws relating to espionage and the national security or the export of technical data. Licensees should apprise themselves of current regulations especially with respect to certain countries, of other agencies, particularly the Office of Defense Trade Controls, Department of State (with respect to Arms, Munitions and Implements of War (22 CFR 121-128)); the Bureau of Industry and Security, Department of Commerce (15 CFR parts 730-774); the Office of Foreign AssetsControl, Department of Treasury (31 CFR Parts 500+) and the Department of Energy.

NOT GRANTED

No license under 35 U.S.C. 184 has been granted at this time, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" DOES NOT appear on this form. Applicant may still petition for a license under 37 CFR 5.12, if a license is desired before the expiration of 6 months from the filing date of the application. If 6 months has lapsed from the filing date of this application and the licensee has not received any indication of a secrecy order under 35 U.S.C. 181, the licensee may foreign file the application pursuant to 37 CFR 5.15(b).

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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
13/683,417	11/21/2012	James S. Baldassarre	26047-0003008

CONFIRMATION NO. 1654

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

POA ACCEPTANCE LETTER

OC000000058174053

Date Mailed: 12/20/2012

NOTICE OF ACCEPTANCE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 11/21/2012.

The Power of Attorney in this application is accepted. Correspondence in this application will be mailed to the above address as provided by 37 CFR 1.33.

/fpan/

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

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minneapolis MN 55440

MAILED
DEC 26 2012
OFFICE OF PETITIONS

Doc Code: TRACK1.GRANT

Decision Granting Request for Prioritized Examination (Track I or After RCE)	Application No.: 13/683,417

1. THE REQUEST FILED November 21, 2012 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 Brian W. Brown at 571-272-5338.

/Brian W. Brown/
[*Signature*]

Petitions Examiner, Office of Petitions
(Title)

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	13683417
	Filing Date	2012-11-21
	First Named Inventor	Baldassarre
	Art Unit	3771
	Examiner Name	
	Attorney Docket Number	26047-0003008

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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
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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]

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	13683417
	Filing Date	2012-11-21
	First Named Inventor	Baldassarre
	Art Unit	3771
	Examiner Name	
	Attorney Docket Number	26047-0003008

	1	U.S. Examiner Ernst V. Arnold, Notice of Abandonment in U.S. Serial No. 12/820,866, mailed December 20, 2012 (2 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.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	13683417
	Filing Date	2012-11-21
	First Named Inventor	Baldassarre
	Art Unit	3771
	Examiner Name	
	Attorney Docket Number	26047-0003008

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)	2012-12-27
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:	14567417
Application Number:	13683417
International Application Number:	
Confirmation Number:	1654
Title of Invention:	METHODS FOR TREATING PATIENTS WHO ARE CANDIDATES FOR INHALED NITRIC OXIDE TREATMENT
First Named Inventor/Applicant Name:	James S. Baldassarre
Customer Number:	94169
Filer:	Janis K. Fraser/Nancy Bechet
Filer Authorized By:	Janis K. Fraser
Attorney Docket Number:	26047-0003008
Receipt Date:	27-DEC-2012
Filing Date:	21-NOV-2012
Time Stamp:	13:52:24
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	Information Disclosure Statement (IDS) Form (SB08)	26047_0003008eighthIDS.pdf	612191 300d850ab082d02160ef1a4672db999bb5e1bd92	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.

2	Non Patent Literature	noticeofaban26047_0003002.pdf	108640 2329bb2549d5f43d35784a428c12cbb3530858d7	no	2

Warnings:

Information:

Total Files Size (in bytes):	720831

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

New Applications Under 35 U.S.C. 111

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

National Stage of an International Application under 35 U.S.C. 371

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

New International Application Filed with the USPTO as a Receiving Office

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

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/683,417	11/21/2012	James S. Baldassarre	26047-0003008	1654

94169 7590 01/11/2013

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

EXAMINER	
ARNOLD, ERNST V	
ART UNIT	PAPER NUMBER
1613	
MAIL DATE	DELIVERY MODE
01/11/2013	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.	Applicant(s)	
	13/683,417	BALDASSARRE ET AL.	
	Examiner	Art Unit	
	ERNST ARNOLD	1613	

-- 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* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, 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 _____.

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) *1-30* 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) *1-30* 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).

a)☐ All b)☐ Some * c)☐ None of:

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/08) Paper No(s)/Mail Date *(8)*.

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

4) ☐ Other: _____.

DETAILED ACTION

Claims 1-30 are pending and under examination.

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 obviousness-type double patenting rejection is appropriate where the conflicting claims 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 conflicting 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.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-30 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over:

1. claims 1-29 of U.S. Patent No. 8282966. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instantly claimed subject matter embraces or is embraced by the patented subject matter. The Patent discloses, for example, in claim 13:

> **13**. A method of treatment comprising:
> (a) performing echocardiography to identify a plurality of children who are in need of 20 ppm inhaled nitric oxide treatment for pulmonary hypertension, wherein the children are not dependent on right-to-left shunting of blood;
> (b) determining that a first child of the plurality has a pulmonary capillary wedge pressure greater than or equal to 20 mm Hg and thus has left ventricular dysfunction, so is at particular risk of pulmonary edema upon treatment with inhaled nitric oxide;
> (c) determining that a second child of the plurality does not have left ventricular dysfunction;
> (d) administering the 20 ppm inhaled nitric oxide treatment to the second child; and
> (e) excluding the first child from treatment with inhaled nitric oxide, based on the determination that the first child has left ventricular dysfunction, so is at particular risk of pulmonary edema upon treatment with inhaled nitric oxide.

. While the patent does not expressly teach discontinuation of the treatment or adverse events in the second patient or the time period of 14 days of administration, such

parameters are obvious to the artisan of inhaled nitric oxide technology due to the inherent physiological actions of NO and the need to look out for patient safety over any time period of administration. Consequently, the ordinary artisan would have recognized the obvious variation of the instant subject matter over the patented subject matter despite the slight changes in language.

2. claims 1-30 of U.S. Patent No. 8293284. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instantly claimed subject matter embraces or is embraced by the patented subject matter. The Patent discloses, for example, in claim 13:

13. A method of treatment comprising:
(a) performing echocardiography to identify a plurality of term or near-term neonate patients who are in need of 20 ppm inhaled nitric oxide treatment for pulmonary hypertension, wherein the patients are not dependent on right-to-left shunting of blood;
(b) determining that a first patient of the plurality has a pulmonary capillary wedge pressure greater than or equal to 20 mm Hg and thus has left ventricular dysfunction, so is at particular risk of pulmonary edema upon treatment with inhaled nitric oxide;
(c) determining that a second patient of the plurality does not have left ventricular dysfunction;
(d) administering the 20 ppm inhaled nitric oxide treatment to the second patient; and
(e) excluding the first patient from treatment with inhaled nitric oxide, based on the determination that the first patient has left ventricular dysfunction, so is at particular risk of pulmonary edema upon treatment with inhaled nitric oxide.

While the patent does not expressly teach discontinuation of the treatment or the time period of 14 days of administration, such parameters are obvious to the artisan of inhaled nitric oxide technology due to the inherent physiological

actions of NO and the need to look out for patient safety over any time period of administration. Consequently, the ordinary artisan would have recognized the obvious variation of the instant subject matter over the patented subject matter despite the slight changes in language.

3. Claims 1-25 of copending application 13/651660. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instantly claimed subject matter embraces or is embraced by the copending subject matter. The copending application discloses, for example, in claim 6:

> 6. A method of treatment comprising:
>
> (a) performing echocardiography to identify a plurality of term or near-term neonate patients who are in need of 20 ppm inhaled nitric oxide treatment for hypoxic respiratory failure, wherein the patients are not dependent on right-to-left shunting of blood;
>
> (b) determining that a first patient of the plurality has left ventricular dysfunction consistent with a pulmonary capillary wedge pressure greater than or equal to 20 mm Hg, so is at particular risk of pulmonary edema upon treatment with inhaled nitric oxide;
>
> (c) determining that a second patient of the plurality does not have left ventricular dysfunction,
>
> (d) administering the 20 ppm inhaled nitric oxide treatment to the second patient; and
>
> (e) excluding the first patient from treatment with inhaled nitric oxide, based on the determination that the first patient has left ventricular dysfunction, so is at particular risk of pulmonary edema upon treatment with inhaled nitric oxide.

While the copending application does not expressly teach discontinuation of the treatment or the time period of 14 days of administration, such parameters are obvious to the artisan of inhaled nitric oxide technology due to the inherent physiological actions of NO and the need to look out for patient safety over any time period of administration. Consequently, the ordinary artisan would have recognized the obvious variation of the

instant subject matter over the copending subject matter despite the slight changes in language.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ERNST 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

EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	8	(((baldassarre or rosskamp or ino).in. or INO.as.) and ((inhale or inhaled) with ((nitric adj oxide) or NO)) and (left with (ventricular or ventricle)) and (hypoxic or hypoxia))	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2013/01/10 09:22
L2	0	(600/483-485.ccls. and ((inhale or inhaled) with ((nitric adj oxide) or NO)) and (left with (ventricular or ventricle)) and (hypoxic or hypoxia))	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2013/01/10 09:24
L3	19	(424/718.ccls. and ((inhale or inhaled) with ((nitric adj oxide) or NO)) and (left with (ventricular or ventricle)) and (hypoxic or hypoxia))	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2013/01/10 09:25
L4	13	l3 and (neonatal or preterm or infant or baby or babies or premie or premature)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2013/01/10 09:28
L5	1	"5904938".pn. and (neonatal or preterm or infant or baby or babies or premie or premature)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2013/01/10 09:30

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99)**		
	Application Number	13683417
	Filing Date	2012-11-21
	First Named Inventor	Baldassarre
	Art Unit	
	Examiner Name	
	Attorney Docket Number	26047-0003008

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	First Named Inventor	Baldassarre
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	Attorney Docket Number	26047-0003008

	1	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)	☐
	2	EP 09251949 Office Action dated 10/11/2010, 5 pages	☐
	3	Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), NCT00005773 at ClinicalTrials.gov (2008)	☐
	4	European Patent Office minutes of oral proceedings in EP 09 251 949.5, with allowable claims (7 pages), dated May 23, 2012	☐
	5	Fauci et al., Harrison's Principles of Internal Medicine, pages1287-1291 and 1360, 12th edition, McGraw Hill (1998)	☐
	6	Federal Regulations 21 CFR Part 312, <<http://www.gcrc.uci.edu/rsa/aer.cfm>>	☐
	7	Ferguson et al., "Inhaled nitric oxide for hypoxemic respiratory failure: Passing bad gas?," Canadian Medical Association Journal, Vol. 162 (1), pages 85-86 (2000)	☐
	8	Field, "Neonatal Ventilation With Inhaled Nitric Oxide Versus Ventilatory Support Without Inhaled Nitric Oxide for Preterm Infants With Severe Respiratory Failure: The INNOVO Multicentre Radomised Controlled Trial (ISRCTN 17821339)," Pediatrics Journal, Vol. 115, pages 926-936 (2005) DOI: 10.1542/peds.2004-1209	☐
	9	Figure from Dr. Green's presentation given 1/10/11; 1 page	☐
	10	Findlay, "Paradoxical Haemodynamic Response to Inhaled Nitric Oxide," International Journal of Intensive Care GB, Vol 5, No. 4, pages 134-139 (1998)	☐
	11	Finer et al., "Randomized, Prospective Study of Low-Dose Versus High-Dose Inhaled Nitric Oxide in the Neonate With Hypoxic Respiratory Failure," Pediatrics, Vol. 108, No. 4, pages 949-955 (2001)	☐

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	12	Fraisse et al., "Acute pulmonary hypertension in infants and children: cGMP-related drugs," Pediatric Crit. Care Med., Vol 11, No. 2 (Suppl.), 4 pages (2010)	☐
	13	Fraisse et al., "Doppler echocardiographic predictors of outcome in newborns with persistent pulmonary hypertension," Cardiol Young. Vol. 14(3), pages 277-83 (2004)	☐
	14	Green, "Patent Ductus Ateriosus Demonstrating Shunting of Blood," Figure from presentation given 1/10/2011	☐
	15	Greenough, "Inhaled nitric oxide in the neonatal period", Expert Opinion on Investigational Drugs, Ashley Publications Ltd., pages 1601-1609 pages (2000)	☐
	16	Guidelines for Industry: Clinical Safety Data Management, <<www.fda.gov/downloads/Drugs/ GuidanceComplianceRegulatoryInformation/Guidance/ucm073087.pdf>>, March 1995, 17 pages	☐
	17	Haddad et al., "Use of inhaled nitric oxide perioperatively and in intensive care patients," Anesthesiology, Vol. 92, pages 1821-1825 (2000)	☐
	18	Hare et al., 'Influence of Inhaled Nitric Oxide on Systemic Flow and Ventricular Filling Pressure in Patients Receiving Mechanical Circulatory Assistance," Circulation, Vol. 95, pages 2250-2253 (1997)	☐
	19	Hayward et al., "Effect of Inhaled Nitric Oxide on Normal Human Left Ventricular Function," JACC, Vol. 30, No. 1, pages 49-56 (1997)	☐
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	23	Headrick, "Hemodynamic monitoring of the critically ill neonate," J. Perinat. Neonatal Nurs., Vol 5(4), pages 58-67 (1992)	☐
	24	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)	☐
	25	Huddleston, "Indications for heart transplantation in children," Progress in Pediatric Cardiology, Vol. 26, pages 3-9 (2009)	☐
	26	Husten, "Dronedarone is Less Effective, But Safer Than Amiodarone in Atrial Fibrillation," page 3, (2009) http://www.npci.org.uk/blog/?p=778	☐
	27	Hurford et al., "Nitric Oxide," Biology and Pathobiology, Academic Press, Chapter 56, pages 931-945 (2000)	☐
	28	Ichinose et al., "Inhaled Nitric Oxide - A Selective Pulmonary Vasodilator: Current Uses and Therapeutic Potential," Circulation, Vol. 109, pages 3106-3111 (2004)	☐
	29	Inglessis et al., "Does inhaled nitric oxide support the hemodynamic of spontaneous breathing patients with cardiogenic shock related to right ventricular myocardial infarction? Reply," JACC, Vol. 45, No. 6, pages 965-966 (2005)	☐
	30	Inglessis et al., "Hemodynamic effects of inhaled nitric oxide in right ventricular myocardial infarction and cardiogenic shock," JACC, Vol. 44, No. 4, pages 793-798 (2004)	☐
	31	Baldassarre, "Inhaled Nitric Oxide (INO) in Hypoxic Respiratory Failure, Study description, study sponsored by INO Therapeutics," ClinicalTrials.gov Identifier NCT00922532, 4 pages (2009)	☐
	32	"Inhaled Nitric Oxide and Hypoxic Respiratory Failure in Infants With Congenital Diaphragmatic Hernia," The Neonatal Inhaled Nitric Oxide Study Group (NINOS), Pediatrics, Vol. 99, No. 6, pages 838-845 (1997)	☐
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	37	INO Therapeutics, LLC, "INOflo for Inhalation 800ppm," package leaflet, 2010	☐
	38	INO Therapeutics, NCT00041548 at ClinicalTrials.gov (2005)	☐
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	40	INOmax (nitric oxide) for inhalation 100 and 800 ppm (parts per million), drug label insert, 2007, 2 pages	☐
	41	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)	☐
	42	James et al., "Treatment of heart failure in children," Current Pediatrics, Vol. 15, 539-548 (2005)	☐
	43	JP 2009157623 Office Action dated 02/15/2011, 3 pages	☐
	44	JP 2009157623 Office Action dated 02/23/2010, 3 pages	☐

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	45	JP 2009157623 Office Action dated 07/30/2010, 6 pages	☐
	46	JP 2009157623 Office Action response filed 06/18/2010, 37 pages (no translation)	☐
	47	JP 2009157623 request for accelerated exam filed 01/15/2010 (60 pages)	☐
	48	JP 2009157623 response filed 11/30/2010, 58 pages	☐
	49	Kay et al., "Congestive heart failure in pediatric patients," From the Department of Pediatrics, Duke University Medical Center, by Mosby, Inc., 6 pages (2001)	☐
	50	Kazerooni et al., "Cardiopulmonary Imaging," Lippincott Williams & Wilkins, pages 234-235 (2 pages) (2004)	☐

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	01/10/2013

*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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	Art Unit		
	Examiner Name		
	Attorney Docket Number	26047-0003008	

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)	2012-12-03
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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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.

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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.

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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.

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Receipt date: 12/04/2012	Application Number	13683417 13683417 - GAU: 1613
INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99)**	Filing Date	2012-11-21
	First Named Inventor	Baldassarre
	Art Unit	
	Examiner Name	
	Attorney Docket Number	26047-0003008

	1	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)	☐
	2	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)	☐
	3	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)	☐
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	5	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)	☐
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	9	Letter of acceptance of AU application 2009202685, dated 08/10/2010, 3 pages	☐
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	12	Lipshultz, "Ventricular dysfunction clinical research in infants, children and adolescents," Progress in Pediatric Cardiology, Vol. 12, pages 1-28 (2000)	☐
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	14	Lipshultz, "Clinical research directions in pediatric cardiology," Current Opinion in Pediatrics, Vol. 21, pages 585-593 (2009)	☐
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	33	Murray, "Angiotensin Converting Enzyme Inhibitory Peptides Derived from Food Proteins: Biochemistry, Bioactivity and Production," Current Pharmaceutical Design, pages 773-791 (2007)	☐

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	Attorney Docket Number	26047-0003008

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	39	NIH Clinical Center, Department Policy and Procedure Manual for the Critical Care Therapy and Respiratory Care Section; Nitric Oxide Therapy, sections 3.1-3.1.2 & 5.2.3 (2000)	☐
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	41	Notification of Reason for Rejection, mailed 7/30/2010, from Japanese Patent Application No. 2009-157623 (cites foreign references)	☐
	42	Office Action for AU 2010202422 dated 07/09/2010, 3 pages	☐
	43	Office Action from AU 2009202685 dated 03/15/2010	☐
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	45	Office Action Response for AU 2009202685 to 03/15/2010 OA, filed 06/08/2010 (16 pages)	☐
	46	Office Action Response for JP2007157623 filed on 11/12/2009 (no English translation)	☐
	47	Office Action Response to AU 2010202422 OA dated 07/09/2010, response filed 09/01/2010	☐
	48	www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidance/ucm073087.pdf, March 1995	☐

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Examiner Signature	/Ernst Arnold/	Date Considered	01/10/2013

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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)	2012-12-04
Name/Print	Janis K. Fraser	Registration Number	34819

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Receipt date: 12/27/2012	Application Number	13683417 13683417 - GAU: 1613
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/E.A./	1	U.S. Examiner Ernst V. Arnold, Notice of Abandonment in U.S. Serial No. 12/820,866, mailed December 20, 2012 (2 pages)	☐

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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.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99)**		
	Application Number	13683417
	Filing Date	2012-11-21
	First Named Inventor	Baldassarre
	Art Unit	
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Receipt date: 12/06/2012	Application Number	13683417 13683417 - GAU: 1613
INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99)**	Filing Date	2012-11-21
	First Named Inventor	Baldassarre
	Art Unit	
	Examiner Name	
	Attorney Docket Number	26047-0003008

	1	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	☐
	2	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)	☐
	3	Barrington et al., "Inhaled nitric oxide for respiratory failure in preterm infants (review)," The Cochrane Collaboration, Wiley Publishers, 3 pages (2009)	☐
	4	Barst, Pediatr., "Vasodilator Testing with Nitric Oxide and/or Oxygen in Pediatric Pulmonary Hypertension," Cardiol., Vol. 31, pages 598-606 (2010)	☐
	5	Macrae, "Drug therapy in persistent pulmonary hypertension of the newborn," Semin. Neonatal, Vol. 2, pages 49-58 (1997)	☐
	6	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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	Examiner Name		
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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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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)	2012-12-06
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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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)).

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	Examiner Name	
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	Attorney Docket Number	26047-0003008

	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 Amendment (Accelerated Exam-Transmittal Amendment/Reply) in U.S. Serial No. 12/820,866 mailed September 23, 2010, 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 Amendment (Accelerated Exam-Transmittal Amendment/Reply) in U.S. Serial No. 12/820,866 mailed November 2, 2010, 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 (Accelerated Exam-Transmittal Amendment/Reply) in U.S. Serial No. 12/820,866 mailed September 23, 2010, filed March 1, 2011 (9 pages)	☐
	9	Lee & Hayes, Reply After Final (Accelerated Exam-Transmittal Amendment/Reply) in U.S. Serial No. 12/820,866 mailed September 23, 2010, filed March 1, 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 (Accelerated Exam-Transmittal Amendment/Reply) in U.S. Serial No. 12/820,866 mailed November 2, 2010, filed May 2, 2011 (9 pages)	☐

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	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, mailed August 17, 2010, 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 (Accelerated Exam-Transmittal Reply) in U.S. Serial No. 12/820,980, mailed November 2, 2010, 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 (Accelerated Exam-Transmittal Reply) in U.S. Serial No. 12/820,980, mailed November 2, 2010, filed May 2, 2011 (23 pages)	☐

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	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, mailed June 10, 2011, 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, mailed August 13, 2010, 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, mailed June 27, 2011, 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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	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 Reply, in U.S. Serial No. 12/821,020, mailed June 15, 2012, 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 Amendment in U.S. Serial No. 12/821,041, mailed August 17, 2010, filed February 14, 2011 (28 pages)	☐
	40	Lee & Hayes, Supplemental Reply Amendment in U.S. Serial No. 12/821,041, mailed August 17, 2010, 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, mailed June 27, 2011, 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., in U.S. Serial No. 12/821,041, Supplemental Amendment and Remarks, filed May 11, 2012 (32 pages)	☐

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	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, mailed June 19, 2012, filed August 15, 2012 (17 pages)	☐
	47	Lee & Hayes Amendment in Reply to Office Action in U.S. Serial No. 12/820,866, mailed June 8, 2011, 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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Signature	/Janis K. Fraser/	Date (YYYY-MM-DD)	2012-12-07
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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.

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	Application Number	13683417
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	First Named Inventor	Baldassarre
	Art Unit	
	Examiner Name	
	Attorney Docket Number	26047-0003008

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	1	5873359		1999-02-23	Zapol et al.	
	2	6063407		2000-05-16	Zapol et al.	
	3	6601580		2003-08-05	Bloch et al.	
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	1	20040106954		2004-06-03	Whitehurst et al.	
	2	20090018136		2009-01-15	Oppenheimer et al.	

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	Attorney Docket Number	26047-0003008

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	1	EP1682672	EP		2006-07-26			☐
	2	WO2005004884	WO		2005-01-20			☐
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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.

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)	2012-11-30
Name/Print	Janis K. Fraser	Registration Number	34819

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SERIAL NUMBER	FILING or 371(c) DATE RULE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
13/683,417	11/21/2012	424	1613	26047-0003008

APPLICANTS

James S. Baldassarre, Doylestown, PA;
Ralf Rosskamp, Chester, NJ;
INO Therapeutics LLC, Hampton, NJ

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

This application is a CON of 12/820,866 06/22/2010 ABN
which is a CON of 12/494,598 06/30/2009 ABN
This application 13/683,417 11/21/2012
is a CON of 13/651,660 10/15/2012
which is a CON of 12/821,041 06/22/2010 PAT 8,293,284
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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
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Inventor Information for 13/683417

Inventor Name	City	State/Country
BALDASSARRE, JAMES S.	DOYLESTOWN	PENNSYLVANIA
ROSSKAMP, RALF	CHESTER	NEW JERSEY
INO THERAPEUTICS LLC	HAMPTON	NEW JERSEY

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Receipt date: 12/05/2012	Application Number	13683417 13683417 - GAU: 1613
INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99)**	Filing Date	2012-11-21
	First Named Inventor	Baldassarre
	Art Unit	
	Examiner Name	
	Attorney Docket Number	26047-0003008

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	Attorney Docket Number	26047-0003008

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

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SIGNATURE

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Signature	/Janis K. Fraser/	Date (YYYY-MM-DD)	2012-12-05
Name/Print	Janis K. Fraser	Registration Number	34819

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	13683417	BALDASSARRE ET AL.
	Examiner	Art Unit
	ERNST ARNOLD	1613

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Class	Subclass	Date	Examiner
424	718 text limited	1/10/13	eva
600	483-485text limited	1/10/13	eva

SEARCH NOTES		
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INTERFERENCE SEARCH			
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99)**		
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/E.A./	1	Fish & Richardson P.C., Supplemental Remarks in U.S. Serial No. 12/821,020, filed May 9, 2012 (22 pages)	☐
/E.A./	2	U.S. Examiner Ernst V. Arnold, Interview Summary in U.S. Serial No. 12/821,020, mailed January 25, 2012 (4 pages)	☐
/E.A./	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)	☐
/E.A./	4	U.S. Examiner Ernst V. Arnold, Examiner's Answer in U.S. Serial No. 12/820,866, mailed November 2, 2011 (27 pages)	☐
/E.A./	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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Name/Print	Janis K. Fraser	Registration Number	34819

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	: James S. Baldassarre et al.	Art Unit	: 1613
Serial No.	: 13/683,417	Examiner	: Ernst V. Arnold
Filed	: November 21, 2012	Conf. No.	: 1654
Title	: METHODS FOR TREATING PATIENTS WHO ARE CANDIDATES FOR INHALED NITRIC OXIDE TREATMENT		

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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 inventors of the present patent application to the current assignee as shown below:

1. From James S. Baldassarre and Ralf Rosskamp to Ikaria Holdings, Inc. The document was recorded in the Patent and Trademark Office at Reel 029352, Frame 0846.

2. From Ikaria Holdings, Inc. to Ikaria, Inc. The document was recorded in the Patent and Trademark Office at Reel 029381, Frame 0216.

3. From Ikaria, Inc. to INO Therapeutics LLC. The document was recorded in the Patent and Trademark Office at Reel 029353, Frame 0634.

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

CERTIFICATE OF (A) MAILING BY FIRST CLASS MAIL OR (B) TRANSMISSION
I hereby certify under 37 CFR §1.8(a) that this correspondence is either (A) addressed as set out in 37 CFR §1.1(a) and being deposited with the United States Postal Service as first class mail with sufficient postage, or (B) being transmitted by facsimile in accordance with 37 CFR § 1.6(d) or via the Office electronic filing system in accordance with 37 CFR § 1.6(a)(4), on the date indicated below.

January 15, 2013
Date of Deposit or Transmission

/Nancy Bechet/
Signature

Nancy Bechet
Typed or Printed Name of Person Signing Certificate

date of the full statutory term of the patent that issues on U.S. application no. 13/651,660. 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 the patent that issues on U.S. application no. 13/651,660.

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 the patent that issues on U.S. application no. 13/651,660 in the event that the latter 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 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 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 patent that issues on U.S. application no. 13/651,660.

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

The fee of $160 is being paid concurrently under 37 C.F.R. § 1.20(d). Apply any necessary charges or credits to Deposit Account 06-1050, referencing the above attorney docket number.

Respectfully submitted,

Date: January 15, 2013

/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

22967714.doc

Electronic Patent Application Fee Transmittal	
Application Number:	13683417
Filing Date:	21-Nov-2012
Title of Invention:	METHODS FOR TREATING PATIENTS WHO ARE CANDIDATES FOR INHALED NITRIC OXIDE TREATMENT
First Named Inventor/Applicant Name:	James S. Baldassarre
Filer:	Janis K. Fraser/Nancy Bechet
Attorney Docket Number:	26047-0003008
Filed as Large 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($)
Miscellaneous:				
Statutory or terminal disclaimer	1814	1	160	160
		Total in USD ($)		**160**

Electronic Acknowledgement Receipt	
EFS ID:	14707479
Application Number:	13683417
International Application Number:	
Confirmation Number:	1654
Title of Invention:	METHODS FOR TREATING PATIENTS WHO ARE CANDIDATES FOR INHALED NITRIC OXIDE TREATMENT
First Named Inventor/Applicant Name:	James S. Baldassarre
Customer Number:	94169
Filer:	Janis K. Fraser/Nancy Bechet
Filer Authorized By:	Janis K. Fraser
Attorney Docket Number:	26047-0003008
Receipt Date:	15-JAN-2013
Filing Date:	21-NOV-2012
Time Stamp:	17:38:19
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$160
RAM confirmation Number	4671
Deposit Account	061050
Authorized User	
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows: Charge any Additional Fees required under 37 C.F.R. Section 1.21 (Miscellaneous fees and charges)	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Terminal Disclaimer Filed	termdiscl_0003008_13651660.pdf	61971 aaa9c4b7c35291cef87407324a2a61a6b7bcb8ef	no	2
Warnings:					
Information:					
2	Fee Worksheet (SB06)	fee-info.pdf	30300 02264e5f6de92bed53e4d4aa25c480cca9112d02	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	92271		

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

Applicant	: James S. Baldassarre et al.	Art Unit	: 1613
Serial No.	: 13/683,417	Examiner	: Ernst V. Arnold
Filed	: November 21, 2012	Conf. No.	: 1654
Title	: METHODS FOR TREATING 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 inventors of the present patent application to the current assignee as shown below:

1. From James S. Baldassarre and Ralf Rosskamp to Ikaria Holdings, Inc. The document was recorded in the Patent and Trademark Office at Reel 029352, Frame 0846.

2. From Ikaria Holdings, Inc. to Ikaria, Inc. The document was recorded in the Patent and Trademark Office at Reel 029381, Frame 0216.

3. From Ikaria, Inc. to INO Therapeutics LLC. The document was recorded in the Patent and Trademark Office at Reel 029353, Frame 0634.

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

CERTIFICATE OF (A) MAILING BY FIRST CLASS MAIL OR (B) TRANSMISSION
I hereby certify under 37 CFR §1.8(a) that this correspondence is either (A) addressed as set out in 37 CFR §1.1(a) and being deposited with the United States Postal Service as first class mail with sufficient postage, or (B) being transmitted by facsimile in accordance with 37 CFR § 1.6(d) or via the Office electronic filing system in accordance with 37 CFR § 1.6(a)(4), on the date indicated below.

January 15, 2013
Date of Deposit or Transmission

/Nancy Bechet/
Signature

Nancy Bechet
Typed or Printed Name of Person Signing Certificate

date of the full statutory term of U.S. Patent No. 8,282,966. 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 U.S. Patent No. 8,282,966.

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 U.S. Patent No. 8,282,966 in the event that U.S. Patent No. 8,282,966 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 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 U.S. Patent No. 8,282,966.

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

The fee of $160 is being paid concurrently under 37 C.F.R. § 1.20(d). Apply any necessary charges or credits to Deposit Account 06-1050, referencing the above attorney docket number.

Respectfully submitted,

Date: January 15, 2013

/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

22967714.doc

Electronic Patent Application Fee Transmittal	
Application Number:	13683417
Filing Date:	21-Nov-2012
Title of Invention:	METHODS FOR TREATING PATIENTS WHO ARE CANDIDATES FOR INHALED NITRIC OXIDE TREATMENT
First Named Inventor/Applicant Name:	James S. Baldassarre
Filer:	Janis K. Fraser/Nancy Bechet
Attorney Docket Number:	26047-0003008
Filed as Large 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($)
Miscellaneous:				
Statutory or terminal disclaimer	1814	1	160	160
		Total in USD ($)		**160**

Electronic Acknowledgement Receipt	
EFS ID:	14707568
Application Number:	13683417
International Application Number:	
Confirmation Number:	1654
Title of Invention:	METHODS FOR TREATING PATIENTS WHO ARE CANDIDATES FOR INHALED NITRIC OXIDE TREATMENT
First Named Inventor/Applicant Name:	James S. Baldassarre
Customer Number:	94169
Filer:	Janis K. Fraser/Nancy Bechet
Filer Authorized By:	Janis K. Fraser
Attorney Docket Number:	26047-0003008
Receipt Date:	15-JAN-2013
Filing Date:	21-NOV-2012
Time Stamp:	17:44:23
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$160
RAM confirmation Number	4762
Deposit Account	061050
Authorized User	
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows: Charge any Additional Fees required under 37 C.F.R. Section 1.21 (Miscellaneous fees and charges)	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Terminal Disclaimer Filed	termdiscl_0003008_8282966.pdf	61861 ba669009fcc3b88013c51e37b570134ff7cf4986	no	2
Warnings:					
Information:					
2	Fee Worksheet (SB06)	fee-info.pdf	30302 487e074ea63109c542141cd464ce4b18fc5b3392	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	92163		

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>
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	: James S. Baldassarre et al.	Art Unit	: 1613
Serial No.	: 13/683,417	Examiner	: Ernst V. Arnold
Filed	: November 21, 2012	Conf. No.	: 1654
Title	: METHODS FOR TREATING PATIENTS WHO ARE CANDIDATES FOR INHALED NITRIC OXIDE TREATMENT		

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

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3. From Ikaria, Inc. to INO Therapeutics LLC. The document was recorded in the Patent and Trademark Office at Reel 029353, Frame 0634.

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.

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CERTIFICATE OF (A) MAILING BY FIRST CLASS MAIL OR (B) TRANSMISSION
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January 15, 2013
Date of Deposit or Transmission

/Nancy Bechet/
Signature

Nancy Bechet
Typed or Printed Name of Person Signing Certificate

date of the full statutory term of U.S. Patent No. 8,293,284. 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 U.S. Patent No. 8,293,284.

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 U.S. Patent No. 8,293,284 in the event that U.S. Patent No. 8,293,284 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 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 U.S. Patent No. 8,293,284.

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

The fee of $160 is being paid concurrently under 37 C.F.R. § 1.20(d). Please apply any necessary charges or credits to Deposit Account 06-1050, referencing the above attorney docket number.

Respectfully submitted,

Date: January 15, 2013

/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

22967714.doc

Electronic Patent Application Fee Transmittal	
Application Number:	13683417
Filing Date:	21-Nov-2012
Title of Invention:	METHODS FOR TREATING PATIENTS WHO ARE CANDIDATES FOR INHALED NITRIC OXIDE TREATMENT
First Named Inventor/Applicant Name:	James S. Baldassarre
Filer:	Janis K. Fraser/Nancy Bechet
Attorney Docket Number:	26047-0003008
Filed as Large 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($)
Miscellaneous:				
Statutory or terminal disclaimer	1814	1	160	160
		Total in USD ($)		**160**

Electronic Acknowledgement Receipt	
EFS ID:	14707623
Application Number:	13683417
International Application Number:	
Confirmation Number:	1654
Title of Invention:	METHODS FOR TREATING PATIENTS WHO ARE CANDIDATES FOR INHALED NITRIC OXIDE TREATMENT
First Named Inventor/Applicant Name:	James S. Baldassarre
Customer Number:	94169
Filer:	Janis K. Fraser/Nancy Bechet
Filer Authorized By:	Janis K. Fraser
Attorney Docket Number:	26047-0003008
Receipt Date:	15-JAN-2013
Filing Date:	21-NOV-2012
Time Stamp:	17:47:42
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$160
RAM confirmation Number	4822
Deposit Account	061050
Authorized User	
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows: Charge any Additional Fees required under 37 C.F.R. Section 1.21 (Miscellaneous fees and charges)	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Terminal Disclaimer Filed	termdiscl_0003008_8293284.pdf	61879 d893d32b31032afa16f3e79d38655be35bdf70aa	no	2
Warnings:					
Information:					
2	Fee Worksheet (SB06)	fee-info.pdf	30300 a999eced02e36ee3c4469947f4670f02101ba967	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	92179		

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
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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
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	: James S. Baldassarre et al.	Art Unit	: 1613
Serial No.	: 13/683,417	Examiner	: Ernst V. Arnold
Filed	: November 21, 2012	Conf. No.	: 1654
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

REPLY TO ACTION OF JANUARY 11, 2013

This application is under Prioritized Examination (Track 1). The following remarks are submitted in response to the Office action mailed January 11, 2013. Applicants also submit an Information Disclosure Statement with the necessary fee.

REMARKS

Claims 1-30 are pending and under examination. No amendments to the claims are presently proposed.

The Office action rejected claims 1-30 on the ground of nonstatutory double patenting over the claims of US Patent Nos. 8,282,966 and 8,293,284, and also over the claims of co-pending application 13/651,660. This is the sole ground of rejection described in the Office action. Without acquiescing in the basis for the rejection, Applicants on January 15, 2013, filed three terminal disclaimers and their applicable fees in the present application, each terminal disclaimer respectively referencing one of the three cited patents/co-pending application. Applicants submit that the terminal disclaimers are sufficient to overcome the rejections. Allowance of the claims is therefore respectfully requested.

If any issues remain, the Examiner is asked to telephone the undersigned to discuss.

No fee is believed due. Apply any necessary charges or credits to Deposit Account 06-1050, referencing the above attorney docket number.

Respectfully submitted,

Date: January 16, 2013

/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

Applicant	: James S. Baldassarre et al.	Art Unit	: 1613
Serial No.	: 13/683,417	Examiner	: Ernst V. Arnold
Filed	: November 21, 2012	Conf. No.	: 1654
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

NINTH INFORMATION DISCLOSURE STATEMENT

Please consider the documents listed on the enclosed SB-08 form.

The following related U.S. applications and patents are brought to the Examiner's attention. Applicants presume that the Examiner (who is handling all of the listed applications) has access to the prosecution documents in each case through the Office's database. Applicants will supply copies of any such prosecution documents upon request.

12/494,598, filed June 30, 2009 (abandoned)
12/820,866, filed June 22, 2010 (abandoned)
12/820,980, filed June 22, 2010 (abandoned)
12/821,020, filed June 22, 2010 (issued as U.S. patent no. 8,282,966)
12/821,041, filed June 22, 2010 (issued as U.S. patent no. 8,293,284)
13/651,660, filed October 15, 2012 (pending)
13/683,236, filed November 21, 2012 (pending)
13/683,444, filed November 21, 2012 (pending)

This statement is being filed after a first Office Action on the merits, but before receipt of a Final Office Action or a Notice of Allowance. Apply $180 in payment of the late submission fee of §1.17(p) and any other necessary charges or credits to Deposit Account 06-1050, referencing the above attorney docket number.

Respectfully submitted,

Date: January 16, 2013

/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

22969458.doc

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

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99)**		
	Application Number	13683417
	Filing Date	2012-11-21
	First Named Inventor	Baldassarre
	Art Unit	1613
	Examiner Name	Ernst V. Arnold
	Attorney Docket Number	26047-0003008

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	5558083		1996-09-24	Bathe et al.	
	2	5651358		1997-07-29	Briend et al.	
	3	6142147		2000-11-07	Head et al.	
If you wish to add additional U.S. Patent citation information please click the Add button.						Add

U.S.PATENT APPLICATION PUBLICATIONS						Remove
Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	20020185126		2002-12-12	Krebs	
	2	20030131848		2003-07-17	Stenzler	
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]

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	13683417
	Filing Date	2012-11-21
	First Named Inventor	Baldassarre
	Art Unit	1613
	Examiner Name	Ernst V. Arnold
	Attorney Docket Number	26047-0003008

	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]
	1		☐

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.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	13683417
	Filing Date	2012-11-21
	First Named Inventor	Baldassarre
	Art Unit	1613
	Examiner Name	Ernst V. Arnold
	Attorney Docket Number	26047-0003008

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)	2013-01-16
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 Patent Application Fee Transmittal					
Application Number:	13683417				
Filing Date:	21-Nov-2012				
Title of Invention:	METHODS FOR TREATING PATIENTS WHO ARE CANDIDATES FOR INHALED NITRIC OXIDE TREATMENT				
First Named Inventor/Applicant Name:	James S. Baldassarre				
Filer:	Janis K. Fraser/Lisa Gray				
Attorney Docket Number:	26047-0003008				
Filed as Large 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($)
Miscellaneous:				
Submission- Information Disclosure Stmt	1806	1	180	180
		Total in USD ($)		**180**

Electronic Acknowledgement Receipt	
EFS ID:	14720870
Application Number:	13683417
International Application Number:	
Confirmation Number:	1654
Title of Invention:	METHODS FOR TREATING PATIENTS WHO ARE CANDIDATES FOR INHALED NITRIC OXIDE TREATMENT
First Named Inventor/Applicant Name:	James S. Baldassarre
Customer Number:	94169
Filer:	Janis K. Fraser/Lisa Gray
Filer Authorized By:	Janis K. Fraser
Attorney Docket Number:	26047-0003008
Receipt Date:	16-JAN-2013
Filing Date:	21-NOV-2012
Time Stamp:	22:03:45
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$180
RAM confirmation Number	8925
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		26047-0003008reply.pdf	66775 c3c5a2e4a006ff5b7ea7f9a85cb652a19ea34beb	yes	2
	Multipart Description/PDF files in .zip description				
	Document Description		**Start**	**End**	
	Amendment/Req. Reconsideration-After Non-Final Reject		1	1	
	Applicant Arguments/Remarks Made in an Amendment		2	2	
Warnings:					
Information:					
2	Transmittal Letter	26047-0003008ids.pdf	64631 0e306761c7f2f78298be36e6bdac933eb5221526	no	2
Warnings:					
Information:					
3	Information Disclosure Statement (IDS) Form (SB08)	26047-0003008sb08.pdf	612295 bd2ddd6eec1c518e68ce9c9190fe24bf27cc6a09	no	4
Warnings:					
Information:					
4	Fee Worksheet (SB06)	fee-info.pdf	30439 c00b76fdbb8e2ea19e4bc8a3d5d6cfc190908a13	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	774140		

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.

Application Number	Application/Control No.	Applicant(s)/Patent under Reexamination	
	13/683,417	BALDASSARRE ET AL.	

Document Code - DISQ	Internal Document – DO NOT MAIL

TERMINAL DISCLAIMER	☒ APPROVED	☐ DISAPPROVED
Date Filed : January 15, 2013	**This patent is subject to a Terminal Disclaimer**	

Approved/Disapproved by:

Henry D. Jefferson

3 td's are approved

U.S. Patent and Trademark Office

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

NOTICE OF ALLOWANCE AND FEE(S) DUE

94169 7590 03/01/2013

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

EXAMINER
ARNOLD, ERNST V

ART UNIT	PAPER NUMBER
1613	

DATE MAILED: 03/01/2013

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/683,417	11/21/2012	James S. Baldassarre	26047-0003008	1654

TITLE OF INVENTION: METHODS FOR TREATING PATIENTS WHO ARE CANDIDATES FOR INHALED NITRIC OXIDE TREATMENT

APPLN. TYPE	SMALL ENTITY	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	NO	$1770	$0	$0	$1770	06/03/2013

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 SMALL ENTITY status shown above.

If the SMALL ENTITY is shown as YES, verify your current SMALL ENTITY status:

A. If the status is the same, pay the TOTAL FEE(S) DUE shown above.

B. If the status above is to be removed, check box 5b on Part B - Fee(s) Transmittal and pay the PUBLICATION FEE (if required) and twice the amount of the ISSUE FEE shown above, or

If the SMALL ENTITY is shown as NO:

A. Pay TOTAL FEE(S) DUE shown above, or

B. If applicant claimed SMALL ENTITY status before, or is now claiming SMALL ENTITY status, check box 5a on Part B - Fee(s) Transmittal and pay the PUBLICATION FEE (if required) and 1/2 the ISSUE FEE shown above.

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**
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 03/01/2013
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.
13/683,417	11/21/2012	James S. Baldassarre	26047-0003008	1654

TITLE OF INVENTION: METHODS FOR TREATING PATIENTS WHO ARE CANDIDATES FOR INHALED NITRIC OXIDE TREATMENT

APPLN. TYPE	SMALL ENTITY	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	NO	$1770	$0	$0	$1770	06/03/2013

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 credit any overpayment, to Deposit Account Number _____ (enclose an extra copy of this form).

5. **Change in Entity Status** (from status indicated above)
- ❑ a. Applicant claims SMALL ENTITY status. See 37 CFR 1.27.
- ❑ b. Applicant is no longer claiming SMALL ENTITY status. See 37 CFR 1.27(g)(2).

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 _____ Date _____

Typed or printed name _____ Registration No. _____

This collection of information 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.

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.
13/683,417	11/21/2012	James S. Baldassarre	26047-0003008	1654

94169 7590 03/01/2013

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

EXAMINER	
ARNOLD, ERNST V	
ART UNIT	PAPER NUMBER
1613	

DATE MAILED: 03/01/2013

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

The Patent Term Adjustment to date is 0 day(s). If the issue fee is paid on the date that is three months after the mailing date of this notice and the patent issues on the Tuesday before the date that is 28 weeks (six and a half months) after the mailing date of this notice, the Patent Term Adjustment will be 0 day(s).

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 Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

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.	Applicant(s)	
	13/683,417	BALDASSARRE ET AL.	
	Examiner	Art Unit	
	ERNST ARNOLD	1613	

-- 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 *1/16/13*.

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 *1-30*. 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).
   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 1/16/13, 12/3/12
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

DETAILED ACTION

Claims 1-30 are pending and under examination.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on 1/16/13 was filed after the mailing date of the Office Action on 1/11/13. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner. Please note that no date was supplied for reference #6 (Federal Regulations 21 CFR Part 312) on the IDS filed 12/3/12 and the URL provided was not functional to determine the date on the website so the Examiner provided the date on which that document was filed in the instant case.

Terminal Disclaimer

The terminal disclaimers filed on 1/15/13 disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of copending application 13/651660 and US Patents 8282966 and 8293284 have been reviewed and are accepted. The terminal disclaimers have been recorded. The rejections are accordingly withdrawn.

Allowable Subject Matter

The following is an examiner's statement of reasons for allowance: Applicant's amendments have overcome the rejections of record. The instantly claimed subject matter is free of the art. See US Patents 8282966 and 8293284 for a complete rationale.

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 1-30 are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ERNST 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
	13683417	BALDASSARRE ET AL.
	Examiner	Art Unit
	ERNST 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	1/10/13	eva
600	483-485text limited	1/10/13	eva

SEARCH NOTES		
Search Notes	Date	Examiner
inventor/assignee name EAST/PALM	1/10/13	eva
EAST all databases	1/10/13	eva
search update EAST all databases	2/14/13	eva
updated IDS	2/14/13	eva

INTERFERENCE SEARCH			
US Class/ CPC Symbol	US Subclass / CPC Group	Date	Examiner
128	200.24 text limited	2/14/13	eva
424	718 text limited	2/14/13	eva
600	483-485 text limited	2/14/13	eva

718	

EAST Search History

EAST Search History (Interference)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L6	0	600/483-485.ccls. and ((inhale or inhaled) with ((nitric adj oxide) or NO)).clm. and ((left with (ventricular or ventricle)) and (hypoxic or hypoxia)).clm.	US-PGPUB; USPAT; UPAD	OR	ON	2013/02/14 11:41
L7	4	424/718.ccls. and ((inhale or inhaled) with ((nitric adj oxide) or NO)).clm. and ((left with (ventricular or ventricle)) and (hypoxic or hypoxia)).clm.	US-PGPUB; USPAT; UPAD	OR	ON	2013/02/14 11:41
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(Not for submission under 37 CFR 1.99)

Application Number	13683417
Filing Date	2012-11-21
First Named Inventor	Baldassarre
Art Unit	1613
Examiner Name	Ernst V. Arnold
Attorney Docket Number	26047-0003008

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	1	5558083		1996-09-24	Bathe et al.	
	2	5651358		1997-07-29	Briend et al.	
	3	6142147		2000-11-07	Head et al.	

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	1	20020185126		2002-12-12	Krebs	
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Receipt date: 01/16/2013	Application Number	13683417
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Examiner Signature	/Ernst Arnold/	Date Considered	02/14/2013

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Receipt date: 01/16/2013	Application Number	13683417
INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99**)	Filing Date	2012-11-21
	First Named Inventor	Baldassarre
	Art Unit	1613
	Examiner Name	Ernst V. Arnold
	Attorney Docket Number	26047-0003008

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)	2013-01-16
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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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.

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	Application Number	13683417
	Filing Date	2012-11-21
	First Named Inventor	Baldassarre
	Art Unit	
	Examiner Name	
	Attorney Docket Number	26047-0003008

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Receipt date: 12/03/2012	Application Number	13683417 13683417 - GAU: 1613
INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99)**	Filing Date	2012-11-21
	First Named Inventor	Baldassarre
	Art Unit	
	Examiner Name	
	Attorney Docket Number	26047-0003008

	1	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)	☐
	2	EP 09251949 Office Action dated 10/11/2010, 5 pages	☐
	3	Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), NCT00005773 at ClinicalTrials.gov (2008)	☐
	4	European Patent Office minutes of oral proceedings in EP 09 251 949.5, with allowable claims (7 pages), dated May 23, 2012	☐
	5	Fauci et al., Harrison's Principles of Internal Medicine, pages1287-1291 and 1360, 12th edition, McGraw Hill (1998)	☐
	6	Federal Regulations 21 CFR Part 312, <<http://www.gcrc.uci.edu/rsa/aer.cfm>> 12/3/12 /EA/	☐
	7	Ferguson et al., "Inhaled nitric oxide for hypoxemic respiratory failure: Passing bad gas?," Canadian Medical Association Journal, Vol. 162 (1), pages 85-86 (2000)	☐
	8	Field, "Neonatal Ventilation With Inhaled Nitric Oxide Versus Ventilatory Support Without Inhaled Nitric Oxide for Preterm Infants With Severe Respiratory Failure: The INNOVO Multicentre Radomised Controlled Trial (ISRCTN 17821339)," Pediatrics Journal, Vol. 115, pages 926-936 (2005) DOI: 10.1542/peds.2004-1209	☐
	9	Figure from Dr. Green's presentation given 1/10/11; 1 page	☐
	10	Findlay, "Paradoxical Haemodynamic Response to Inhaled Nitric Oxide," International Journal of Intensive Care GB, Vol 5, No. 4, pages 134-139 (1998)	☐
	11	Finer et al., "Randomized, Prospective Study of Low-Dose Versus High-Dose Inhaled Nitric Oxide in the Neonate With Hypoxic Respiratory Failure," Pediatrics, Vol. 108, No. 4, pages 949-955 (2001)	☐

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	First Named Inventor	Baldassarre
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	Attorney Docket Number	26047-0003008

	12	Fraisse et al., "Acute pulmonary hypertension in infants and children: cGMP-related drugs," Pediatric Crit. Care Med., Vol 11, No. 2 (Suppl.), 4 pages (2010)	☐
	13	Fraisse et al., "Doppler echocardiographic predictors of outcome in newborns with persistent pulmonary hypertension," Cardiol Young. Vol. 14(3), pages 277-83 (2004)	☐
	14	Green, "Patent Ductus Ateriosus Demonstrating Shunting of Blood," Figure from presentation given 1/10/2011	☐
	15	Greenough, "Inhaled nitric oxide in the neonatal period", Expert Opinion on Investigational Drugs, Ashley Publications Ltd., pages 1601-1609 pages (2000)	☐
	16	Guidelines for Industry: Clinical Safety Data Management, <<www.fda.gov/downloads/Drugs/ GuidanceComplianceRegulatoryInformation/Guidance/ucm073087.pdf>>, March 1995, 17 pages	☐
	17	Haddad et al., "Use of inhaled nitric oxide perioperatively and in intensive care patients," Anesthesiology, Vol. 92, pages 1821-1825 (2000)	☐
	18	Hare et al., 'Influence of Inhaled Nitric Oxide on Systemic Flow and Ventricular Filling Pressure in Patients Receiving Mechanical Circulatory Assistance," Circulation, Vol. 95, pages 2250-2253 (1997)	☐
	19	Hayward et al., "Effect of Inhaled Nitric Oxide on Normal Human Left Ventricular Function," JACC, Vol. 30, No. 1, pages 49-56 (1997)	☐
	20	Hayward et al., "Inhaled Nitric Oxide in Cardiac Failure: Vascular Versus Ventricular Effects," Journal of Cardiovascular Pharmacology, Vol. 27, pages 80-85, ABSTRACT ONLY (1996)	☐
	21	Hayward et al., "Left Ventricular Chamber Function During Inhaled Nitric Oxide in Patients with Dilated Cardiomyopathy," J. Cardiovascular Pharmacology, Vol. 34, Iss. 5, pages 749-754, ABSTRACT (1999)	☐
	22	Hayward et al., "Inhaled nitric oxide in cardiology practice," Cardiovascular Research, Vol. 43, pages 628-638 (1999)	☐

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	Attorney Docket Number	26047-0003008

	23	Headrick, "Hemodynamic monitoring of the critically ill neonate," J. Perinat. Neonatal Nurs., Vol 5(4), pages 58-67 (1992)	☐
	24	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)	☐
	25	Huddleston, "Indications for heart transplantation in children," Progress in Pediatric Cardiology, Vol. 26, pages 3-9 (2009)	☐
	26	Husten, "Dronedarone is Less Effective, But Safer Than Amiodarone in Atrial Fibrillation," page 3, (2009) http://www.npci.org.uk/blog/?p=778	☐
	27	Hurford et al., "Nitric Oxide," Biology and Pathobiology, Academic Press, Chapter 56, pages 931-945 (2000)	☐
	28	Ichinose et al., "Inhaled Nitric Oxide - A Selective Pulmonary Vasodilator: Current Uses and Therapeutic Potential," Circulation, Vol. 109, pages 3106-3111 (2004)	☐
	29	Inglessis et al., "Does inhaled nitric oxide support the hemodynamic of spontaneous breathing patients with cardiogenic shock related to right ventricular myocardial infarction? Reply," JACC, Vol. 45, No. 6, pages 965-966 (2005)	☐
	30	Inglessis et al., "Hemodynamic effects of inhaled nitric oxide in right ventricular myocardial infarction and cardiogenic shock," JACC, Vol. 44, No. 4, pages 793-798 (2004)	☐
	31	Baldassarre, "Inhaled Nitric Oxide (INO) in Hypoxic Respiratory Failure, Study description, study sponsored by INO Therapeutics," ClinicalTrials.gov Identifier NCT00922532, 4 pages (2009)	☐
	32	"Inhaled Nitric Oxide and Hypoxic Respiratory Failure in Infants With Congenital Diaphragmatic Hernia," The Neonatal Inhaled Nitric Oxide Study Group (NINOS), Pediatrics, Vol. 99, No. 6, pages 838-845 (1997)	☐
	33	Inhaled Nitric Oxide by Oxygen Hood in Neonates, from ClinicalTrials.gov, NCT00732537, 08/08/2008	☐

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	34	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)	☐
	35	Inhaled Nitric Oxide in Neonates with Elevated A-a DO2 Gradients Not Requiring Mechanical Ventilation, from ClinicalTrials.gov archive, NCT00041548, 06/23/2005, 2 pages	☐
	36	INO Therapeutics, "Comparison of Inhaled Nitric Oxide and Oxygen in Patient Reactivity during Acute Pulmonary Vasodilator Testing," downloaded from clinicaltrials.gov on April 23, 2012; first received on February 20, 2008; last updated on October 18, 2010	☐
	37	INO Therapeutics, LLC, "INOflo for Inhalation 800ppm," package leaflet, 2010	☐
	38	INO Therapeutics, NCT00041548 at ClinicalTrials.gov (2005)	☐
	39	INO Thereapeutics, NCT00551642 at ClinicalTrials.gov (2007)	☐
	40	INOmax (nitric oxide) for inhalation 100 and 800 ppm (parts per million), drug label insert, 2007, 2 pages	☐
	41	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)	☐
	42	James et al., "Treatment of heart failure in children," Current Pediatrics, Vol. 15, 539-548 (2005)	☐
	43	JP 2009157623 Office Action dated 02/15/2011, 3 pages	☐
	44	JP 2009157623 Office Action dated 02/23/2010, 3 pages	☐

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	Art Unit	
	Examiner Name	
	Attorney Docket Number	26047-0003008

	45	JP 2009157623 Office Action dated 07/30/2010, 6 pages	☐
	46	JP 2009157623 Office Action response filed 06/18/2010, 37 pages (no translation)	☐
	47	JP 2009157623 request for accelerated exam filed 01/15/2010 (60 pages)	☐
	48	JP 2009157623 response filed 11/30/2010, 58 pages	☐
	49	Kay et al., "Congestive heart failure in pediatric patients," From the Department of Pediatrics, Duke University Medical Center, by Mosby, Inc., 6 pages (2001)	☐
	50	Kazerooni et al., "Cardiopulmonary Imaging," Lippincott Williams & Wilkins, pages 234-235 (2 pages) (2004)	☐

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EXAMINER SIGNATURE

Examiner Signature	/Ernst Arnold/	Date Considered	01/10/2013

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Receipt date: 12/03/2012	Application Number	13683417	13683417 - GAU: 1613
INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99**)	Filing Date	2012-11-21	
	First Named Inventor	Baldassarre	
	Art Unit		
	Examiner Name		
	Attorney Docket Number	26047-0003008	

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)	2012-12-03
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./

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13683417	BALDASSARRE ET AL.
	Examiner	Art Unit
	ERNST ARNOLD	1613

CPC		
Symbol	Type	Version

CPC Combination Sets				
Symbol	Type	Set	Ranking	Version

US ORIGINAL CLASSIFICATION		INTERNATIONAL CLASSIFICATION									
CLASS	SUBCLASS	CLAIMED					NON-CLAIMED				
424	718	A	6	1	B	5 / 02 (2006.01.01)	A	6	1	M	16 / 00 (2006.01.01)
CROSS REFERENCE(S)		A	0	1	N	59 / 00 (2006.01.01)					
		A	6	1	K	33 / 00 (2006.01.01)					
CLASS	SUBCLASS (ONE SUBCLASS PER BLOCK)	C	0	1	B	21 / 24 (2006.01.01)					
128	200.24										
423	405										

NONE		Total Claims Allowed:	
(Assistant Examiner)	(Date)	30	
/ERNST ARNOLD/ Primary Examiner.Art Unit 1613	2/14/13	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	none

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13683417	BALDASSARRE ET AL.
	Examiner	**Art Unit**
	ERNST ARNOLD	1613

600	483	484	485												

NONE (Assistant Examiner)	(Date)	**Total Claims Allowed:** 30	
/ERNST ARNOLD/ Primary Examiner.Art Unit 1613 (Primary Examiner)	2/14/13 (Date)	O.G. Print Claim(s) 1	O.G. Print Figure none

U.S. Patent and Trademark Office

Part of Paper No. 20130209

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13683417	BALDASSARRE ET AL.
	Examiner	**Art Unit**
	ERNST 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 ARNOLD/ Primary Examiner.Art Unit 1613 (Primary Examiner)	2/14/13 (Date)	O.G. Print Claim(s) 1	O.G. Print Figure none

U.S. Patent and Trademark Office Part of Paper No. 20130209

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13683417	BALDASSARRE ET AL.
	Examiner	Art Unit
	ERNST 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	02/14/2013								
	1	=								
	2	=								
	3	=								
	4	=								
	5	=								
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	8	=								
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	26	=								
	27	=								
	28	=								
	29	=								
	30	=								

EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	2	"5558083".pn.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2013/02/14 11:37
L2	2	"5651358".pn.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2013/02/14 11:37
L3	2	"6142147".pn.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2013/02/14 11:38
L4	2	"20020185126".pn.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2013/02/14 11:39
L5	2	"20030131848".pn.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2013/02/14 11:39
S1	8	(((baldassarre or rosskamp or ino).in. or INO.as.) and ((inhale or inhaled) with ((nitric adj oxide) or NO)) and (left with (ventricular or ventricle)) and (hypoxic or hypoxia))	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2013/01/10 09:22
S2	0	(600/483-485.ccls. and ((inhale or inhaled) with ((nitric adj oxide) or NO)) and (left with (ventricular or ventricle)) and (hypoxic or hypoxia))	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2013/01/10 09:24
S3	19	(424/718.ccls. and ((inhale or inhaled) with ((nitric adj oxide) or NO)) and (left with (ventricular or ventricle)) and (hypoxic or hypoxia))	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2013/01/10 09:25
S4	13	S3 and (neonatal or preterm or infant or baby or babies or premie or premature)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2013/01/10 09:28
S5	1	"5904938".pn. and (neonatal or preterm or infant or baby or babies or premie or premature)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2013/01/10 09:30

S6	6	(128/200.24.ccls. and ((inhale or inhaled) with ((nitric adj oxide) or NO)) and (left with (ventricular or ventricle)) and (hypoxic or hypoxia))	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2013/01/10 14:14

2/ 14/ 2013 11:42:17 AM
C:\ Users\ earnold\ Documents\ EAST\ Workspaces\ 13683417.wsp

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	: James S. Baldassarre et al.	Art Unit :	1613
Serial No.	: 13/683,417	Examiner :	Ernst V. Arnold
Filed	: November 21, 2012	Confirmation No.:	1654
		Notice of Allowance Date: March 1, 2013	
Title	: METHODS FOR TREATING PATIENTS WHO ARE CANDIDATES FOR INHALED NITRIC OXIDE TREATMENT		

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

RESPONSE TO NOTICE OF ALLOWANCE MAILED MARCH 1, 2013

A completed Part B - Fee(s) Transmittal is enclosed.

Comments on Statement of Reasons for Allowance

The Examiner's statement of reasons for allowance says, "Applicant's amendments have overcome the rejections of record." Applicant notes that no amendments were filed in this application. The sole rejections of record in this application were for nonstatutory double patenting, and were overcome by the submission of appropriate terminal disclaimers.

The statement of reasons for allowance also notes "The instantly claimed subject matter is free of the art. See US Patents 8282966 and 8293284 for a complete rationale." It is recognized that in accordance with M.P.E.P. § 1302.14, the Examiner's reasons for allowance need not set forth all of the details as to why the claims are allowed. In the present application, it is not conceded that the rationale stated in the reasons for allowance in US patents 8282966 and 8293284, or anywhere else in the prosecution history of US patents 8282966 and 8293284,

CERTIFICATE OF (A) MAILING BY FIRST CLASS MAIL OR (B) TRANSMISSION
I hereby certify under 37 CFR §1.8(a) that this correspondence is either (A) addressed as set out in 37 CFR §1.1(a) and being deposited with the United States Postal Service as first class mail with sufficient postage, or (B) being transmitted by facsimile in accordance with 37 CFR § 1.6(d) or via the Office electronic filing system in accordance with 37 CFR § 1.6(a)(4), on the date indicated below.

March 8, 2013
Date of Deposit or Transmission

/Nancy Bechet/
Signature

Nancy Bechet
Typed or Printed Name of Person Signing Certificate

provide a "complete rationale" for why the present claims are allowable. The limitations in the claims of those two patents, including limitations identified in the reasons for allowance of the two patents, are not identical to the limitations in the present claims. In addition, at least some of the present claims include limitations that are not found in the claims of US patent 8282966 or 8293284, and that provide additional bases for patentability over the art of record.

The required fee of $1770 is being paid with this filing. Apply any other necessary charges or credits to Deposit Account 06-1050, referencing the above attorney docket number.

Respectfully submitted,

Date: March 8, 2013

/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

22993768.doc

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 03/01/2013

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.
13/683,417	11/21/2012	James S. Baldassarre	26047-0003008	1654

TITLE OF INVENTION: METHODS FOR TREATING PATIENTS WHO ARE CANDIDATES FOR INHALED NITRIC OXIDE TREATMENT

APPLN. TYPE	SMALL ENTITY	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	NO	$1770	$0		$1770	06/03/2013

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):
[ ] 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)
[ ] a. Applicant claims SMALL ENTITY status. See 37 CFR 1.27. [ ] b. Applicant is no longer claiming SMALL ENTITY status. See 37 CFR 1.27(g)(2).

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 March 8, 2013

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

22993783.doc

Electronic Patent Application Fee Transmittal

Application Number:	13683417
Filing Date:	21-Nov-2012
Title of Invention:	METHODS FOR TREATING PATIENTS WHO ARE CANDIDATES FOR INHALED NITRIC OXIDE TREATMENT
First Named Inventor/Applicant Name:	James S. Baldassarre
Filer:	Janis K. Fraser/Nancy Bechet
Attorney Docket Number:	26047-0003008

Filed as Large 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:				
Utility Appl Issue Fee	1501	1	1770	1770
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
			Total in USD ($)	**1770**

Electronic Acknowledgement Receipt	
EFS ID:	15156268
Application Number:	13683417
International Application Number:	
Confirmation Number:	1654
Title of Invention:	METHODS FOR TREATING PATIENTS WHO ARE CANDIDATES FOR INHALED NITRIC OXIDE TREATMENT
First Named Inventor/Applicant Name:	James S. Baldassarre
Customer Number:	94169
Filer:	Janis K. Fraser/Paul Stovenour
Filer Authorized By:	Janis K. Fraser
Attorney Docket Number:	26047-0003008
Receipt Date:	08-MAR-2013
Filing Date:	21-NOV-2012
Time Stamp:	14:04:18
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$1770
RAM confirmation Number	414
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	Issue Fee Payment (PTO-85B)	respnoa260470003008.pdf	111601 d560dc2b603d850b491250c56b810a6e07e1283a	no	3
Warnings:					
Information:					
2	Fee Worksheet (SB06)	fee-info.pdf	30465 c9fc9e0749278bf86f0e37186c1e9e0a0d631797	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	142066		

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.

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 NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
13/683,417	11/21/2012	James S. Baldassarre	26047-0003008

CONFIRMATION NO. 1654

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

PUBLICATION NOTICE

OC000000060120618

Title:METHODS FOR TREATING PATIENTS WHO ARE CANDIDATES FOR INHALED NITRIC OXIDE TREATMENT

Publication No.US-2013-0078321-A1
Publication Date:03/28/2013

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

UNITED STATES PATENT AND TRADEMARK OFFICE

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

APPLICATION NO.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/683,417	04/30/2013	8431164	26047-0003008	1654

94169 7590 04/10/2013

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):

James S. Baldassarre, Doylestown, PA;
Ralf Rosskamp, Chester, NJ;
INO Therapeutics LLC, Hampton, NJ

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
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.

Request for Continued Examination (RCE) Transmittal

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

Application Number	13/683,417
Filing Date	November 21, 2012
First Named Inventor	James S. Baldassarre
Art Unit	1613
Examiner Name	Ernst V. Arnold
Attorney Docket Number	26047-0003008

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 Petition to Withdraw from Issuance, QPIDS Form SB09, and four references

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	April 11, 2013
Name (Print/Type)	Janis K. Fraser, Ph.D., J.D.	Registration No.	34,819

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	13683417
	Filing Date	2012-11-21
	First Named Inventor	Baldassarre
	Art Unit	1613
	Examiner Name	Ernst V. Arnold
	Attorney Docket Number	26047-0003008

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

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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]
	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	13683417
	Filing Date	2012-11-21
	First Named Inventor	Baldassarre
	Art Unit	1613
	Examiner Name	Ernst V. Arnold
	Attorney Docket Number	26047-0003008

	1	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)	☒
	2	Communication from Canadian Intellectual Property Office dated March 19, 2013, enclosing Protest from Robic regarding Canadian patent application no. 2,671,029 (42 pages)	☐
	3	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)	☐
	4	Hess, "Heliox and Inhaled Nitric Oxide," Mechanical Ventilation, Chapter 28 (2001), pages 454-480	☐

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.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	13683417
	Filing Date	2012-11-21
	First Named Inventor	Baldassarre
	Art Unit	1613
	Examiner Name	Ernst V. Arnold
	Attorney Docket Number	26047-0003008

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)	2013-03-26
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 Patent Application Fee Transmittal

Application Number:	13683417
Filing Date:	21-Nov-2012
Title of Invention:	METHODS FOR TREATING PATIENTS WHO ARE CANDIDATES FOR INHALED NITRIC OXIDE TREATMENT
First Named Inventor/Applicant Name:	James S. Baldassarre
Filer:	Timothy A. French
Attorney Docket Number:	26047-0003008

Filed as Large Entity

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Petition fee- 37 CFR 1.17(h) (Group III)	1464	1	140	140
Request for Continued Examination	1801	1	1200	1200
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Miscellaneous:				
			Total in USD ($)	**1340**

UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450
www.uspto.gov

Decision Date : April 11, 2013

In re Application of :

James Baldassarre

DECISION ON PETITION

UNDER CFR 1.313(c)(2)

Application No : 13683417

Filed : 21-Nov-2012

Attorney Docket No : 26047-0003008

This is an electronic decision on the petition under 37 CFR 1.313(c)(2), filed April 11, 2013 , 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:	15493083
Application Number:	13683417
International Application Number:	
Confirmation Number:	1654
Title of Invention:	METHODS FOR TREATING PATIENTS WHO ARE CANDIDATES FOR INHALED NITRIC OXIDE TREATMENT
First Named Inventor/Applicant Name:	James S. Baldassarre
Customer Number:	94169
Filer:	Timothy A. French
Filer Authorized By:	
Attorney Docket Number:	26047-0003008
Receipt Date:	11-APR-2013
Filing Date:	21-NOV-2012
Time Stamp:	15:02:20
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$1340
RAM confirmation Number	1421
Deposit Account	061050
Authorized User	
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows: Charge any Additional Fees required under 37 C.F.R. Section 1.21 (Miscellaneous fees and charges)	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Petition automatically granted by EFS	petition-request.pdf	31782 0c910e9edac40e26032a2455f9a8678b4a9285b5	no	2
Warnings:					
Information:					
2	Transmittal Letter	PETwithdraw_26047_0003008.pdf	61193 854740f28eac82bfafb9cd5b807e89075bed4d82	no	1
Warnings:					
Information:					
3	Request for Continued Examination (RCE)	RCE26047_0003008.pdf	141726 9698ae8eda108a86ead5e74d89b161f6dc0ee495	no	1
Warnings:					
This is not a USPTO supplied RCE SB30 form.					
Information:					
4	Quick Path Information Disclosure Statement	SB09_26047_0003008.pdf	74262 9cf4dcbdbb75649fa05b834bf14e4bf1aa1d52c8	no	2
Warnings:					
Information:					
5	Information Disclosure Statement (IDS) Form (SB08)	QPIDSSB08_26047_0003008.pdf	612459 eb78cd57bd045292f660419718c37937f43016c1	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.					
6	Non Patent Literature	frenchrefenglishtrans.pdf	2291043 d71ea21c6061443f110143b3c49acabecaee6b99	no	37
Warnings:					
Information:					
7	Non Patent Literature	Hess.pdf	5443748 9d3b97f03c1d9a306d2fc4221eeda6c4e7aa2277	no	28
Warnings:					
Information:					

8	Non Patent Literature	ProtestRobic.pdf	4045379 24008447a33d1b35e43c82f384d090af5a2ab737	no	42
Warnings:					
Information:					
9	Non Patent Literature	ProtestTorys.pdf	5472833 ef4a7327814f284e845a869b1e8aa57494904946	no	36
Warnings:					
Information:					
10	Fee Worksheet (SB06)	fee-info.pdf	32103 6f27b0aa30c26ff3f80dfd103fe04c558358dcd7	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	18206528		

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.

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	13683417
Filing Date	21-Nov-2012
First Named Inventor	James Baldassarre
Art Unit	1613
Examiner Name	ERNST ARNOLD
Attorney Docket Number	26047-0003008
Title	METHODS FOR TREATING 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

☐ Applicant claims SMALL ENTITY status. See 37 CFR 1.27.

☐ Applicant is no longer claiming SMALL ENTITY status. See 37 CFR 1.27(g)(2).

☐ Applicant(s) status remains as SMALL ENTITY.

☒ Applicant(s) status remains as other than SMALL ENTITY

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 ◯ A joint inventor; all of whom are signing this e-petition ◯ The assignee of record of the entire interest that has properly made itself of record pursuant to 37 CFR 3.71

Signature	/timothy a. french/
Name	/timothy a. french/
Registration Number	30175

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	: James S. Baldassarre et al.	Art Unit	: 1613
Serial No.	: 13/683,417	Examiner	: Ernst V. Arnold
Filed	: November 21, 2012	Conf. No.	: 1654
Title	: METHODS FOR TREATING PATIENTS WHO ARE CANDIDATES FOR INHALED NITRIC OXIDE TREATMENT		

MAIL STOP 313 (c)
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

PETITION UNDER 37 CFR 1.313(C)

Applicant hereby petitions under §1.313(c)(2) for the withdrawal of this application from issue to permit consideration of an Information Disclosure Statement. The issue fee was paid on March 8, 2013.

A request for continued examination (RCE), form PTO SB-08 (IDS), and form PTO SB-09 (Certification and Request for Consideration of an Information Disclosure Statement Filed after Payment of the Issue Fee under the QPIDS Pilot Program) are being filed at this time, with the necessary fees. The RCE is intended to continue this application upon the grant of this petition and the decision of the Office to reopen prosecution.

The petition fee required by 1.17(h) is being paid with this petition. Apply that and any other necessary charges or credits to Deposit Account 06-1050, referencing the above attorney docket number.

Respectfully submitted,

Date: April 11, 2013

/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

23008878.doc

CERTIFICATE OF (A) MAILING BY FIRST CLASS MAIL OR (B) TRANSMISSION
I hereby certify under 37 CFR §1.8(a) that this correspondence is either (A) addressed as set out in 37 CFR §1.1(a) and being deposited with the United States Postal Service as first class mail with sufficient postage, or (B) being transmitted by facsimile in accordance with 37 CFR § 1.6(d) or via the Office electronic filing system in accordance with 37 CFR § 1.6(a)(4), on the date indicated below.

April 11, 2013
Date of Deposit or Transmission

/Nancy Bechet/
Signature

Nancy Bechet
Typed or Printed Name of Person Signing Certificate

Document code: WFEE

United States Patent and Trademark Office
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01 FC : 1806 180.00 DA

Document code: WFEE

United States Patent and Trademark Office
Sales Receipt for Accounting Date: 12/23/2013

KTURNER ADJ #00000011 Mailroom Dt: 04/11/2013
Seq No: 1 Sales Acctg Dt: 04/15/2013 061050 13683417
01 FC : 1806 180.00 CR

Receipt date: 04/11/2013

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	13683417
Filing Date	2012-11-21
First Named Inventor	Baldassarre
Art Unit	1613
Examiner Name	Ernst V. Arnold
Attorney Docket Number	26047-0003008

U.S.PATENTS Remove

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

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

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							☐

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]

Receipt date: 04/11/2013		
INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)	Application Number	13683417
	Filing Date	2012-11-21
	First Named Inventor	Baldassarre
	Art Unit	1613
	Examiner Name	Ernst V. Arnold
	Attorney Docket Number	26047-0003008

/E.A./	1	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)	☒
/E.A./	2	Communication from Canadian Intellectual Property Office dated March 19, 2013, enclosing Protest from Robic regarding Canadian patent application no. 2,671,029 (42 pages)	☐
/E.A./	3	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)	☐
/E.A./	4	Hess, "Heliox and Inhaled Nitric Oxide," Mechanical Ventilation, Chapter 28 (2001), pages 454-480	☐

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	04/12/2013

*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.

Receipt date: 04/11/2013	Application Number	13683417
INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)	Filing Date	2012-11-21
	First Named Inventor	Baidassarre
	Art Unit	1613
	Examiner Name	Ernst V. Arnold
	Attorney Docket Number	26047-0003008

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)	2013-03-26
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.**

Receipt date: 04/11/2013

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.

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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.

U.S. DEPARTMENT OF COMMERCE
PATENT AND TRADEMARK OFFICE

PATENT WITHDRAWAL NOTICE

DATE WITHDRAWN	WITHDRAWAL NUMBER
4/16/2013	22381

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

4/30/2013 issue.

SERIAL NO.	PATENT NUMBER
13/683,417	8,431,164
DRAWINGS	**CLASS**
000	424/718

TITLE

METHODS FOR TREATING PATIENTS WHO ARE CANDIDATES FOR INHALED NITRIC OXIDE TREATMENT

NAME AND ADDRESS

JAMES S. BALDASSARRE, ET AL
DOYLESTOWN, PA

REASON FOR WITHDRAWAL

Office of Petitions granted applicant's request to withdraw patent from issue.
AUTO-PETITION

APPROVED

/Kimberly Terrell/, Manager

Patent Publication Branch
Office of Data Management

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

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

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99)**		
	Application Number	13683417
	Filing Date	2012-11-21
	First Named Inventor	Baldassarre
	Art Unit	1613
	Examiner Name	Ernst V. Arnold
	Attorney Docket Number	26047-0003008

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

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	13683417
	Filing Date	2012-11-21
	First Named Inventor	Baldassarre
	Art Unit	1613
	Examiner Name	Ernst V. Arnold
	Attorney Docket Number	26047-0003008

	1	Free Merriam-Webster Dictionary, definition of "supplying", pages 1-4, downloaded April 22, 2013	☐
	2	Himashree et al., "Nitric oxide and the respiratory system," Current Science, Vol. 85, No. 5, September 10, 2003, pages 607-614	☐
	3	Kazerooni, Cardiopulmonary Imaging 2004, Lippincott Williams & Wilkins, "Left Ventricular Function", pages 234 and 236 (in part)	☐
	4	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	☐
	5	Loh et al., "Cardiovascular Effects of Inhaled Nitric Oxide in Patients With Left Ventricular Dysfunction," Circulation, Vol. 90, pages 2780-2785 (1994)	☐
	6	McLaughlin et al., "Pulmonary Arterial Hypertension," Circulation, Vol. 114, pages 1417-1431 (2006)	☐

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EXAMINER SIGNATURE

Examiner Signature		Date Considered	

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	Art Unit	1613
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	Attorney Docket Number	26047-0003008

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Signature	/Janis K. Fraser/	Date (YYYY-MM-DD)	2013-04-29
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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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:	15636785
Application Number:	13683417
International Application Number:	
Confirmation Number:	1654
Title of Invention:	METHODS FOR TREATING PATIENTS WHO ARE CANDIDATES FOR INHALED NITRIC OXIDE TREATMENT
First Named Inventor/Applicant Name:	James S. Baldassarre
Customer Number:	94169
Filer:	Janis K. Fraser/Nancy Bechet
Filer Authorized By:	Janis K. Fraser
Attorney Docket Number:	26047-0003008
Receipt Date:	29-APR-2013
Filing Date:	21-NOV-2012
Time Stamp:	14:45:30
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	Non Patent Literature	freemerriam.pdf	240604 f2b93df7d99ea3ee3a7a4aaa7c65d044e52637c6	no	4

Warnings:
Information:

2	Non Patent Literature	Himashree.pdf	831681 37d636512cee5034df9ed3566b3872309f89e616	no	8
Warnings:					
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3	Non Patent Literature	Kazeroonie.pdf	164234 03d8748cc487b5fc7f43151d82f150f40d8c3491	no	2
Warnings:					
Information:					
4	Non Patent Literature	Leo.pdf	1857067 704abf3892145e2e546c5759d60ace49beff08bc	no	11
Warnings:					
Information:					
5	Non Patent Literature	Loh.pdf	1122620 d0a5dd66ea97358a6e4b6075112309b814bf1b9a	no	7
Warnings:					
Information:					
6	Non Patent Literature	McLaughlin.pdf	1694184 5a7ea6f26904f50db74e1aa77627e74cdac5b6f9	no	16
Warnings:					
Information:					
7	Information Disclosure Statement (IDS) Form (SB08)	SBO80003006_ninth.pdf	612630 93e19fe075f233e50ec992f790386b18ccfde482	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.					
		Total Files Size (in bytes):	6523020		

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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
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Attorney Docket No.: 26047-0003008
Client Ref. No.: 3000-US-0008CON6

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	: James S. Baldassarre	Art Unit	: 1613
Serial No.	: 13/683,417	Examiner	: Ernst V. Arnold
Filed	: November 21, 2012	Conf. No.	: 1654
Title	: METHODS FOR TREATING PATIENTS WHO ARE CANDIDATES FOR INHALED NITRIC OXIDE TREATMENT		

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

REQUEST TO CORRECT INVENTORSHIP UNDER 37 C.F.R. § 1.48(A)

Please correct the inventorship for the application referenced above to exclude Ralf Rosskamp. Enclosed is a Supplemental Application Data Sheet in accordance with 37 C.F.R. § 1.76, identifying James S. Baldassarre as the sole inventor.

Apply the processing fee of $140 required by 37 C.F.R. § 1.17(i)(1), the additional fee of $600 required by 37 C.F.R. § 1.17(d), and any other necessary charges or any credits to Deposit Account No. 06-1050, referencing the above attorney docket number.

Respectfully submitted,

Date: December 3, 2013

/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

23123033.doc

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	26047-0003008
	Application Number	13/683,417
Title of Invention	METHODS FOR TREATING PATIENTS WHO ARE CANDIDATES FOR INHALED NITRIC OXIDE TREATMENT	

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.

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.

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	US

Mailing Address of Inventor:

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

Inventor 2.

Prefix	Given Name	Middle Name	Family Name	Suffix
	~~Ralf~~		~~Rosskamp~~	

Residence Information (Select One) ☒ US Residency ☐ Non US Residency ☐ Active US Military Service

City	~~Chester~~	State/Province	~~NJ~~	Country of Residence	~~US~~

Mailing Address of Inventor:

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	26047-0003008
	Application Number	13/683,417
Title of Invention	METHODS FOR TREATING PATIENTS WHO ARE CANDIDATES FOR INHALED NITRIC OXIDE TREATMENT	

Address 1	~~1 Byron Court~~		
Address 2			
City	~~Chester~~	**State/Province**	~~NJ~~
Postal Code	~~07930~~	**Country**	~~US~~

Signature:

A signature of the applicant or representative is required in accordance with 37 CFR 1.33 and 10.18. Please see 37 CFR 1.4(d) for the form of the signature.					
Signature	/Janis Fraser/			Date (**MM/DD/YYYY**)	12/03/2013
First Name	Janis	Last Name	Fraser	Registration Number	34,819

Electronic Patent Application Fee Transmittal

Application Number:	13683417
Filing Date:	21-Nov-2012
Title of Invention:	METHODS FOR TREATING PATIENTS WHO ARE CANDIDATES FOR INHALED NITRIC OXIDE TREATMENT
First Named Inventor/Applicant Name:	James S. Baldassarre
Filer:	Janis K. Fraser/Rita Liston
Attorney Docket Number:	26047-0003008

Filed as Large Entity

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
PROCESSING FEE, EXCEPT PROV. APPLS.	1830	1	140	140
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
Correction of Inventorship on Merits	1819	1	600	600
		Total in USD ($)		**740**

Electronic Acknowledgement Receipt	
EFS ID:	17547781
Application Number:	13683417
International Application Number:	
Confirmation Number:	1654
Title of Invention:	METHODS FOR TREATING PATIENTS WHO ARE CANDIDATES FOR INHALED NITRIC OXIDE TREATMENT
First Named Inventor/Applicant Name:	James S. Baldassarre
Customer Number:	94169
Filer:	Janis K. Fraser/Rita Liston
Filer Authorized By:	Janis K. Fraser
Attorney Docket Number:	26047-0003008
Receipt Date:	03-DEC-2013
Filing Date:	21-NOV-2012
Time Stamp:	10:32:06
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$740
RAM confirmation Number	11718
Deposit Account	061050
Authorized User	
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows: Charge any Additional Fees required under 37 C.F.R. Section 1.21 (Miscellaneous fees and charges)	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Request under Rule 48 correcting inventorship	26047_0003008_Request_Corr_Inv.pdf	47438 cbcfc294677ddd0f2037fbb8adbf28a7366552e8	no	1
Warnings:					
Information:					
2	Application Data Sheet	26047_0003008_supp_ADS.pdf	82301 838c6b559ec53619318d4234159663651f38332e	no	2
Warnings:					
Information:					
This is not an USPTO supplied ADS fillable form					
3	Fee Worksheet (SB06)	fee-info.pdf	32195 a5df4155adc08f3eeea067f000474b9ded3ed0bf	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	161934		

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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>
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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
13/683,417	11/21/2012	1613	2180	26047-0003008	30	3

CONFIRMATION NO. 1654

REPLACEMENT FILING RECEIPT

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

OC000000065375333

Date Mailed: 12/12/2013

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 12/820,866 06/22/2010 ABN
which is a CON of 12/494,598 06/30/2009 ABN
This application 13/683,417
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

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: 12/14/2012
The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 13/683,417**
Projected Publication Date: Not Applicable

Non-Publication Request: No

Early Publication Request: No

Title

METHODS FOR TREATING PATIENTS WHO ARE CANDIDATES FOR INHALED NITRIC OXIDE TREATMENT

Preliminary Class

424

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	Application Number	13683417
	Filing Date	2012-11-21
	First Named Inventor	Baldassarre
	Art Unit	1613
	Examiner Name	
	Attorney Docket Number	26047-0003008

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	First Named Inventor	Baldassarre
	Art Unit	1613
	Examiner Name	
	Attorney Docket Number	26047-0003008

	1	Canadian Intellectual Property Office, Requisition by the examiner in CA Appl. 2,671,029; Apr. 25, 2013; 24 pp.	☐
	2	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	☐
	3	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)	☐
	4	Description of the clinical trial NCT00626028 published online on the website http://clinicaltrials.gov/archive/NCT00626028; Feb. 28, 2008.	☐
	5	Bernasconi et al.; Inhaled Nitric Oxide Applications in Peadiatric Practice, Images in Pediatric Cardiology, Vol. 4(1), Jan-Mar 2002; pages 4-29.	☐
	6	Torys LLP, Letter to Canadian Commissioner of Patents relating to CA 2,671,029; Aug. 9, 2013;	☐
	7	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)	☐
	8	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)	☐
	9	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)	☐
	10	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	☐
	11	Weinberger et al., Pulmonary Hypertension, Chapter 14 of Principles of Pulmonary Medicine, Elsevier Saunders, 2014; pp 189-200	☐

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	13683417
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	First Named Inventor	Baldassarre
	Art Unit	1613
	Examiner Name	
	Attorney Docket Number	26047-0003008

	12	Hayward et al., Inhaled nitric oxide in cardiology practice; Cardiovascular Research 43:628-638 (1999)	☐
	13		☐

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	Application Number	13683417
	Filing Date	2012-11-21
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	Art Unit	1613
	Examiner Name	
	Attorney Docket Number	26047-0003008

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☐ See attached certification statement.

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

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Signature	/Janis K. Fraser/	Date (YYYY-MM-DD)	2013-12-12
Name/Print	Janis K. Fraser	Registration Number	34819

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EFS ID:	17641519
Application Number:	13683417
International Application Number:	
Confirmation Number:	1654
Title of Invention:	METHODS FOR TREATING PATIENTS WHO ARE CANDIDATES FOR INHALED NITRIC OXIDE TREATMENT
First Named Inventor/Applicant Name:	James S. Baldassarre
Customer Number:	94169
Filer:	Janis K. Fraser/Rita Liston
Filer Authorized By:	Janis K. Fraser
Attorney Docket Number:	26047-0003008
Receipt Date:	12-DEC-2013
Filing Date:	21-NOV-2012
Time Stamp:	14:33:31
Application Type:	Utility under 35 USC 111(a)

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99)**		
	Application Number	13683417
	Filing Date	2012-11-21
	First Named Inventor	Baldassarre
	Art Unit	1613
	Examiner Name	Ernst V. Arnold
	Attorney Docket Number	26047-0003008

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	Examiner Name	Ernst V. Arnold
	Attorney Docket Number	26047-0003008

	1	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)	☐
	2	BURKHOFF et al., "Why does pulmonary venous pressure rise after onset of LV dysfunction: a theoretical analysis," Am. J. Physiol., 34:H1819-H1828 (1993)	☐
	3	Prior art notice issued in CA267102 on August 9, 2013 (51 pages)	☐
	4	FROMM et al., "Congestive Heart Failure and Pulmonary Edema for the Emergency Physician," The Journal of Emergency Medicine, 13(1):71-87 (1995)	☐
	5	MOURANI et al., "Left Ventricular Diastolic Dysfunction in Bronchopulmonary Dysplasia," J. of Pediatrics, 152:291-293 (2008)	☐

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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)	2014-05-13
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:

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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.

Electronic Acknowledgement Receipt	
EFS ID:	19022381
Application Number:	13683417
International Application Number:	
Confirmation Number:	1654
Title of Invention:	METHODS FOR TREATING 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:	26047-0003008
Receipt Date:	13-MAY-2014
Filing Date:	21-NOV-2012
Time Stamp:	17:19:09
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	Information Disclosure Statement (IDS) Form (SB08)	SB08.pdf	612585 5c692d08713e44fab678256d2ddcd47b24660ec6	no	4

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2	Non Patent Literature	NEJM.pdf	720985 26219627ef58639fe98446352e64d3a714b573e3	no	8
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4	Non Patent Literature	Fromm.pdf	1739308 44d129171b2b76d7ffad6d7c08a48dba930bc9b7	no	17
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Warnings:					
Information:					
6	Non Patent Literature	Mourani.pdf	113674 3825dcc4bcac966875905a4db2eb0de58bdbf27b	no	3
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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

Applicant	: INO THERAPEUTICS LLC	Art Unit	: 1613
Serial No.	: 13/683,417	Examiner	: Ernst V. Arnold
Filed	: November 21, 2012	Conf. No.	: 1654
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

PRELIMINARY AMENDMENT

This application was withdrawn from issue on April 11, 2013, in order to file an Information Disclosure Statement. A communication from Examiner Arnold dated April 22, 2013, stated that prosecution has been re-opened. No further Office action has been received. Prior to further examination, applicant requests that the following amendment be entered and the remarks and enclosed evidence be made of record.

List of claims (replacing prior versions).

1. (Currently amended) A method of treating patients who are candidates for inhaled nitric oxide treatment, which method reduces the risk that inhalation of nitric oxide gas will induce an increase in pulmonary capillary wedge pressure (PCWP) leading to pulmonary edema in neonatal patients with hypoxic respiratory failure, the method comprising:

(a) ~~performing at least one diagnostic process to identify~~identifying a plurality of term or near-term neonatal patients who have hypoxic respiratory failure and are candidates for 20 ppm inhaled nitric oxide treatment~~, wherein the patients are not dependent on right-to-left shunting of blood~~;

(b) determining that a first patient of the plurality does not have left ventricular dysfunction;

(c) determining that a second patient of the plurality has left ventricular dysfunction, so is at particular risk of increased PCWP leading to pulmonary edema upon treatment with inhaled nitric oxide;

(d) administering 20 ppm inhaled nitric oxide treatment to the first patient; and

(e) excluding the second patient from treatment with inhaled nitric oxide, based on the determination that the second patient has left ventricular dysfunction, so is at particular risk of increased PCWP leading to pulmonary edema upon treatment with inhaled nitric oxide.

2. (Original) The method of claim 1, wherein the first patient has congenital heart disease.

3. (Original) The method of claim 1, wherein the left ventricular dysfunction of the second patient is attributable to congenital heart disease.

4. (Original) The method of claim 1, wherein the second patient is determined to be at particular risk not only of increased PCWP leading to pulmonary edema, but also of other serious adverse events, upon treatment with inhaled nitric oxide, and the second patient is excluded from inhaled nitric oxide treatment based on the determination that the second patient has left ventricular dysfunction and so is at particular risk not only of increased PCWP leading to

pulmonary edema, but also other serious adverse events, upon treatment with inhaled nitric oxide.

5. (Original) The method of claim 4, wherein the left ventricular dysfunction of the second patient is attributable to congenital heart disease.

6. (Original) The method of claim 1, wherein determining that the first patient does not have pre-existing left ventricular dysfunction and the second patient does have pre-existing left ventricular dysfunction comprises performing at least one diagnostic process on each of the first and second patients.

7. (Original) The method of claim 1, wherein determining that the first patient does not have pre-existing left ventricular dysfunction and the second patient does have pre-existing left ventricular dysfunction comprises performing echocardiography on the first and second patients.

8. (Original) The method of claim 1, wherein the second patient has a PCWP that is greater than or equal to 20 mm Hg.

9. (Currently amended) A method of treating patients who are candidates for inhaled nitric oxide treatment, which method reduces the risk that inhalation of the nitric oxide gas will induce an increase in PCWP leading to pulmonary edema in neonatal patients with hypoxic respiratory failure, said method comprising:

(a) ~~performing at least one diagnostic process to identify~~identifying a plurality of term or near-term neonatal patients who have hypoxic respiratory failure and are candidates for 20 ppm inhaled nitric oxide treatment~~, wherein the patients are not dependent on right-to-left shunting of blood~~;

(b) determining that a first patient of the plurality does not have left ventricular dysfunction;

(c) determining that a second patient of the plurality has left ventricular dysfunction, so is at particular risk of increased PCWP leading to pulmonary edema upon treatment with inhaled nitric oxide;

(d) administering 20 ppm inhaled nitric oxide treatment to the first patient; and

(e) excluding the second patient from treatment with inhaled nitric oxide based on the determination in (c), or, despite the second patient's ongoing need for inhaled nitric oxide treatment for hypoxic respiratory failure, discontinuing the second patient's treatment with inhaled nitric oxide after it was begun, the discontinuation being in view of the determination in (c).

10. (Original) The method of claim 9, wherein the discontinuation is in view of both the determination in (c) and the second patient's experiencing an adverse event upon treatment with inhaled nitric oxide.

11. (Original) The method of claim 10, wherein the adverse event comprises pulmonary edema.

12. (Original) The method of claim 10, wherein the adverse event comprises at least one of increased PCWP, systemic hypotension, bradycardia, or cardiac arrest.

13. (Original) The method of claim 9, wherein (c) comprises determining that the second patient has a pulmonary capillary wedge pressure that is greater than or equal to 20 mm Hg.

14. (Original) The method of claim 9, wherein the first patient has congenital heart disease.

15. (Original) The method of claim 9, wherein the left ventricular dysfunction of the second patient is attributable to congenital heart disease.

16. (Original) The method of claim 14, wherein the left ventricular dysfunction of the second patient is attributable to congenital heart disease.

17. (Original) The method of claim 9, wherein

the second patient is determined to be at particular risk not only of increased PCWP leading to pulmonary edema, but also of other serious adverse events, upon treatment with inhaled nitric oxide; and

either (i) the second patient is excluded from inhaled nitric oxide treatment based on both the determination in (c) and the determination that the second patient is also at risk of other serious adverse events upon treatment with inhaled nitric oxide; or (ii) despite the second patient's ongoing need for inhaled nitric oxide treatment for hypoxic respiratory failure, the second patient's treatment with inhaled nitric oxide is discontinued after it was begun, the discontinuation being in view of both the determination in (c) and the determination that the second patient is also at risk of other serious adverse events upon treatment with inhaled nitric oxide.

18. (Original) The method of claim 17, wherein the other serious adverse events comprise one or more of increased PCWP, systemic hypotension, bradycardia, or cardiac arrest.

19. (Original) The method of claim 17, wherein the discontinuation is in view of: the determination in (c), the determination that the second patient is also at risk of other serious adverse events, and the second patient's experiencing an adverse event upon treatment with inhaled nitric oxide.

20. (Original) The method of claim 19, wherein the adverse event experienced by the second patient comprises pulmonary edema.

21. (Original) The method of claim 19, wherein the adverse event experienced by the second patient comprises at least one of increased PCWP, systemic hypotension, bradycardia, or cardiac arrest.

22. (Original) The method of claim 9, wherein determining that the first patient does not have pre-existing left ventricular dysfunction and the second patient does have pre-existing left ventricular dysfunction comprises performing at least one diagnostic process on each of the first and second patients.

23. (Original) The method of claim 9, wherein determining that the first patient does not have pre-existing left ventricular dysfunction and the second patient does have pre-existing left ventricular dysfunction comprises performing echocardiography on each of the first and second patients.

24. (Currently amended) A method of treating patients who are candidates for inhaled nitric oxide treatment, which method reduces the risk of inducing an increase in PCWP leading to pulmonary edema in neonatal patients with hypoxic respiratory failure, the method comprising:

(a) ~~performing at least one diagnostic process to identify~~identifying a plurality of term or near-term neonatal patients who have hypoxic respiratory failure and are candidates for 20 ppm inhaled nitric oxide treatment~~, wherein the patients are not dependent on right-to-left shunting of blood~~;

(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 increased PCWP leading to pulmonary edema upon treatment with inhaled nitric oxide; and

(e) 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.

25. (Original) The method of claim 24, wherein the second treatment regimen does not comprise administration of inhaled nitric oxide.

26. (Original) The method of claim 24, wherein the second treatment regimen comprises beginning administration of inhaled nitric oxide but discontinuing the administration upon determination that inhaling nitric oxide has increased the second patient's PCWP and/or induced pulmonary edema in the second patient.

27. (Original) The method of claim 24, wherein the first patient has congenital heart disease.

28. (Original) The method of claim 24, wherein the pre-existing left ventricular dysfunction of the second patient is attributable to congenital heart disease.

29. (Original) The method of claim 24, wherein the diagnostic process comprises echocardiography.

30. (Original) The method of claim 24, wherein the second patient has a pulmonary capillary wedge pressure that is greater than or equal to 20 mm Hg.

31. (New) The method of claim 1, wherein identifying the plurality of term or near-term neonatal patients who have hypoxic respiratory failure and are candidates for 20 ppm inhaled nitric oxide treatment comprises performing at least one diagnostic process.

32. (New) The method of claim 9, wherein identifying the plurality of term or near-term neonatal patients who have hypoxic respiratory failure and are candidates for 20 ppm inhaled nitric oxide treatment comprises performing at least one diagnostic process.

33. (New) The method of claim 24, wherein identifying the plurality of term or near-term neonatal patients who have hypoxic respiratory failure and are candidates for 20 ppm inhaled nitric oxide treatment comprises performing at least one diagnostic process.

34. (New) A method of treating patients who are candidates for inhaled nitric oxide treatment, which method reduces the risk that inhalation of nitric oxide gas will induce an increase in pulmonary capillary wedge pressure (PCWP) leading to pulmonary edema, the method comprising:

(a) identifying a plurality of patients who are children with a condition that makes them candidates for 20 ppm inhaled nitric oxide treatment;

(b) determining that a first patient of the plurality does not have left ventricular dysfunction;

(c) determining that a second patient of the plurality has left ventricular dysfunction, so is at particular risk of increased PCWP leading to pulmonary edema upon treatment with inhaled nitric oxide;

(d) administering 20 ppm inhaled nitric oxide treatment to the first patient; and

(e) excluding the second patient from treatment with inhaled nitric oxide, based on the determination that the second patient has left ventricular dysfunction, so is at particular risk of increased PCWP leading to pulmonary edema upon treatment with inhaled nitric oxide.

35. (New) The method of claim 34, wherein the second patient is determined to be at particular risk not only of increased PCWP leading to pulmonary edema, but also of other serious adverse events, upon treatment with inhaled nitric oxide, and the second patient is excluded from inhaled nitric oxide treatment based on the determination that the second patient has left ventricular dysfunction and so is at particular risk not only of increased PCWP leading to pulmonary edema, but also other serious adverse events, upon treatment with inhaled nitric oxide.

36. (New) The method of claim 34, wherein the left ventricular dysfunction of the second patient is attributable to congenital heart disease.

37. (New) A method of treating patients who are candidates for inhaled nitric oxide treatment, which method reduces the risk that inhalation of the nitric oxide gas will induce an increase in PCWP leading to pulmonary edema in neonatal patients with hypoxic respiratory failure, said method comprising:

(a) identifying a plurality of patients who are children with a condition that makes them candidates for 20 ppm inhaled nitric oxide treatment;

(b) determining that a first patient of the plurality does not have left ventricular dysfunction;

(c) determining that a second patient of the plurality has left ventricular dysfunction, so is at particular risk of increased PCWP leading to pulmonary edema upon treatment with inhaled nitric oxide;

(d) administering 20 ppm inhaled nitric oxide treatment to the first patient; and

(e) excluding the second patient from treatment with inhaled nitric oxide based on the determination in (c), or, despite the second patient's ongoing need for inhaled nitric oxide treatment for hypoxic respiratory failure, discontinuing the second patient's treatment with inhaled nitric oxide after it was begun, the discontinuation being in view of the determination in (c).

38. (New) The method of claim 37, wherein the discontinuation is in view of both the determination in (c) and the second patient's experiencing an adverse event upon treatment with inhaled nitric oxide.

39. (New) The method of claim 38, wherein the adverse event comprises pulmonary edema.

40. (New) The method of claim 38, wherein the adverse event comprises at least one of increased PCWP, systemic hypotension, bradycardia, or cardiac arrest.

41. (New) The method of claim 37, wherein the left ventricular dysfunction of the second patient is attributable to congenital heart disease.

42. (New) The method of claim 37, wherein

the second patient is determined to be at particular risk not only of increased PCWP leading to pulmonary edema, but also of other serious adverse events, upon treatment with inhaled nitric oxide; and

either (i) the second patient is excluded from inhaled nitric oxide treatment based on both the determination in (c) and the determination that the second patient is also at risk of other serious adverse events upon treatment with inhaled nitric oxide; or (ii) despite the second patient's ongoing need for inhaled nitric oxide treatment for hypoxic respiratory failure, the second patient's treatment with inhaled nitric oxide is discontinued after it was begun, the discontinuation being in view of both the determination in (c) and the determination that the second patient is also at risk of other serious adverse events upon treatment with inhaled nitric oxide.

43. (New) The method of claim 42, wherein the other serious adverse events comprise one or more of increased PCWP, systemic hypotension, bradycardia, or cardiac arrest.

44. (New) The method of claim 42, wherein the discontinuation is in view of: the determination in (c), the determination that the second patient is also at risk of other serious adverse events, and the second patient's experiencing an adverse event upon treatment with inhaled nitric oxide.

REMARKS

Upon entry of the above amendment, claims 1-44 will be pending, new claims 31-44 having been added and no claims canceled. Independent claims 1, 9 and 24 are presently amended. The limitation regarding a "diagnostic process" that is deleted from each of claims 1, 9 and 24 now appears in new dependent claims 31-33. Applicants have also deleted the limitation "wherein the patients are not dependent on right-to-left shunting of blood" from each of claims 1, 9 and 24. New claims 34-44 are based on original claims 1, 4, 5, 9-12, 15, and 17-19, respectively. New independent claims 34 and 37 are based on amended independent claims 1 and 9, respectively, but recite "children with a condition that makes them candidates for 20 ppm inhaled nitric oxide treatment" instead of "term or near-term neonatal patients who have hypoxic respiratory failure and are candidates for 20 ppm inhaled nitric oxide treatment." Support for the limitation about children and a condition that makes them candidates for 20 ppm inhaled nitric oxide treatment can be found throughout the specification, e.g., at [0007], [0015], [0018], [0020], [0023], and [0033]. No new matter has been added. All of the claims are fully entitled to the earliest priority date of this application, i.e., June 30, 2009.

Applicant filed an Information Disclosure Statement on April 11, 2013, along with a petition to withdraw the present application from issue. One of the references cited on that Information Disclosure Statement was "**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)**." The Office later cited that reference ("VasoKINOX") as the primary reference in an obviousness rejection in a related application, USSN 13/683,236, which (like the present case) claims priority back to an application filed on June 30, 2009 (USSN 12/494,598). VasoKINOX bears a date of July 14, 2008, i.e., less than a year before the June 30, 2009 priority date, so does not qualify as prior art under 35 USC § **102(b)** against any application in this family of applications. Applicant responded to the obviousness rejection in '236 by filing both (a) arguments addressing the substance of the rejection and (b) a Declaration under 37 CFR § 1.131 establishing that the inventions encompassed by the claims of '236 had been conceived and reduced to practice before July 14, 2008. Accordingly, VasoKINOX is not citable as

35 USC § **102(a)** prior art against the claims of '236. In case the Office is contemplating citing VasoKINOX against the present claims, applicant submits with this Preliminary Amendment a similar Declaration under 37 CFR § 1.131 proving a date of invention before July 14, 2008. This Declaration should be sufficient to ensure that VasoKINOX is not citable as prior art against the present claims.

Apply any necessary charges or credits to Deposit Account 06-1050, referencing the above attorney docket number.

Respectfully submitted,

Date: May 29, 2014

/Janis K. Fraser/
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	: INO Therapeutics LLC	Art Unit	: 1613
Serial No.	: 13/683,417	Examiner	: Ernst V. Arnold
Filed	: November 21, 2012	Conf. No.	: 1654
Title	: METHODS OF DISTRIBUTING A PHARMACEUTICAL PRODUCT COMPRISING NITRIC OXIDE GAS FOR INHALATION		

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. 13/683,417 (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. Application No. 12/820,866, filed June 22, 2010, and now abandoned, which is a continuation of U.S. Application No. 12/494,598, filed June 30, 2009, and now abandoned. This application is also a continuation of U.S. Application No. 13/651,660 (now U.S. Patent No. 8,431,163), filed October 15, 2012, which is a continuation of U.S. Application No. 12/821,041 (now U.S. Patent No. 8,293,284), filed June 22, 2010, which is a continuation of U.S. Application 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 a document that purports to be a 2008 Belgian marketing authorization for a nitric oxide gas product with the trade name "VasoKINOX". This VasoKINOX document, which was cited in an Information Disclosure Statement filed in the

present application on April 11, 2013, as "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)," bears the date 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.

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 email exchange between me and Debra A. Rimar with a draft Clinical Study Report[1] attached (Appendix 5); and the prescribing information for INOmax® (nitric oxide) for inhalation published in 2007 (Appendix 6). Certain material

[1] 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.

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:

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 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. 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 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®.

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: 21 May 2014

James S. Baldassarre, M.D.

131 declaration 003008

APPENDIX 1

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

2. SYNOPSIS

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

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

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

Criteria for evaluation:

Primary endpoint:

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

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

1) a decrease in PAPm $\geq$ 20% and no decrease in cardiac index (within 5%)

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

1) a decrease in PAPm $\geq$ 20% and no decrease in cardiac index (within 5%)

or

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

Secondary endpoints:

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

Safety endpoints:

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

3. TABLE OF CONTENTS

4. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

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

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

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

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

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

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

Fick Equation:

By measuring the amount of oxygen consumed by the tissues and the arterial-venous oxygen content difference, the cardiac output can be determined.
Fick equation:
$CO = VO_2/min / CaO_2 - CvO_2$
VO_2/min = total tissue extraction of oxygen per minute
CaO_2 = arterial content of oxygen (mL/L)
CvO_2 = venous content oxygen (mL/L)
(CaO_2 may be SaO_2 and CvO_2 may be SvO_2)

Pulmonary Vascular Resistance (PVR):

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

Normal range: 〈 2 units. The PVR is a useful parameter in assessing right ventricular afterload.
(dynes/sec/cm^3 = Woods unit (Hg/L/min)/80)

Pulmonary Vascular Resistance Index (PVRI):

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

PVRI = (PAPm – PAWP)/CI

Pulmonary Hypertension:

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

Reversible Pulmonary Hypertension

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

1) a decrease in PAPm $\geq$ 20% and no decrease in cardiac index (within 5%)

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

1) a decrease in PAPm $\geq$ 20% and no decrease in cardiac index (within 5%)

or

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

5. ETHICS

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

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

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

5.2 Ethical Conduct of the Study

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

5.3 Patient Information and Informed Consent

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

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

5.4 Financial Interest Statement

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

6. INVESTIGATORS AND STUDY ADMINISTRATION STRUCTURE

6.1 Investigators

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

6.2 Administrative Structure

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

6.3 Steering Committee Members

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

6.4 Data Safety and Monitoring Board Members

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

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

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

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

7. INTRODUCTION

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

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

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

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

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

8. STUDY OBJECTIVES

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

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

1) a decrease in PAPm $\geq$ 20% and no decrease in cardiac index (within 5%)

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

1) a decrease in PAPm $\geq$ 20% and no decrease in cardiac index (within 5%)

or

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

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

9. INVESTIGATIONAL PLAN

9.1 Overall Study Plan and Design

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

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

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

9.2 Discussion of Study Design

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

9.3 Selection of Study Population

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

9.3.1 Inclusion Criteria

The patient must meet the following criteria:

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

c. Cardiomyopathy

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

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

9.3.2 Exclusion Criteria

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

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

9.3.3 Removal of Patients from Therapy or Assessment

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

9.4 Treatments

9.4.1 Treatments Administered

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

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

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

9.4.2 Identity of Investigational Product

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

9.4.3 Method of Assigning Patients to Treatment Groups

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

9.4.4 Selection of Doses in the Study

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

9.4.5 Selection and Timing of Dose for Each Patient

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

9.4.6 Treatment Group Assignment Blinding

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

9.4.7 Prior and Concomitant Therapy

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

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

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

9.4.8 Treatment Compliance

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

9.5 Efficacy and Safety Variables

9.5.1 Efficacy and Safety Schedule of Assessments

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

Table 1. Schedule of Assessments

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

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

Table 2. Schedule of Treatments

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

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

9.5.2 Data Collection

Baseline Measurements

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

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

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

Measurements Following First Treatment Administration

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

Measurements Following Second Treatment Administration

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

Measurements Following Third Treatment Administration

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

Measurements 1 year after the diagnostic procedure

- Therapies received since the diagnostic procedure

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

Procedures for Maintenance of Baseline Oxygen Saturation Levels

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

Awake Sedation Patients

Patients Not on Supplemental O_2

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

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

Patients on Supplemental O_2

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

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

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

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

Patients Intubated and Under General Anesthesia

Patients Not on Supplemental O_2

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

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

Patients on Supplemental O_2

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

9.5.3 Ventilator Weaning and Extubation Strategy

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

9.5.4 Appropriateness of Measurements

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

9.5.5 Efficacy Variables

Primary endpoint:

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

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

1) a decrease in PAPm $\geq$ 20% and no decrease in cardiac index (within 5%)

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

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

or

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

Secondary endpoints:

1) Number of patients receiving NO versus the number of patients receiving O_2 that meet response criteria, as defined above.

2) Number of patients receiving a combination of NO and O_2 versus the number of patients receiving NO alone that meet response criteria, as defined above.3) PVRI, PAPm and Cardiac Index readings in Room Air versus NO alone, O_2 alone and the combination of NO and O_2.

4) Change in the ratio of PAPm to SAPm by treatment

5) Survival at 1 year, by response

9.5.6 Safety Variables

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

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

9.5.7 Drug Concentration Measurements

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

9.6 Data Quality Assurance

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

9.7 Statistical Methods Planned and Determination of the Sample Size

See Appendix 2.

9.7.1 Sample Size Determination

The following assumptions are made:

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

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

9.7.2 Interim Analysis

No interim analysis is planned for this trial.

9.8 Changes in Conduct of the Study or Planned Analyses

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

10. ADMINISTRATIVE DETAILS

10.1 Accountability of Study Drug and Equipment

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

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

10.2 Case Report Forms

All case report forms are to be completed within one month after patient completion of the study. A case report form is provided for each patient. All forms are to be filled out in black ink or typed.

Correction(s) of data on the case report form should be made by crossing out the incorrect data (in a manner that leaves the previous entry identifiable) and writing the correct values next to those crossed out. Each correction must be initialed and dated by the individual making the correction.

10.3 Investigator Requirements

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

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

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

10.4 Recording of Adverse Events

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

10.4.1 Study Drug Relationship

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

Not Related

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

Remote

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

Possible

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

Probable

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

Highly Probable

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

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

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

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

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

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

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

10.4.2 Serious Adverse Events

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

Catherine Evans

INO Therapeutics Regualtory Affairs Associate

Phone: +001 908 238-6655

Fax: +001 908 238-6635

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

James S. Baldassarre, MD

INO Therapeutics Senior Director of Research & Development

Phone: +001 908 238-6363

Cell: +001 908 500-8111

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

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

10.4.3 Unexpected Adverse Events

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

10.5 Records Retention

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

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

10.6 Monitoring and Audits

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

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

10.7 Amendments to the Protocol

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

10.8 Termination of Trial

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

11. REFERENCE LIST

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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.
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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
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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)

1

5) When we have agreement on these issues, the protocol will be amended.

6) Final note: Jim Baldassarre to meet with Dr Barst re: longer term follow up of kids in this study.

Dr James S. Baldassarre
Sr Director, Clinical Research
INO Therapeutics LLC
O: 908-238-6363
C: 908-500-8111

APPENDIX 3

TITLE:	**Comparison of Supplemental Oxygen and Nitric Oxide for Inhalation Plus Oxygen in the Evaluation of the Reactivity of the Pulmonary Vasculature During Acute Pulmonary Vasodilator Testing**
DRUG:	INOmax® (nitric oxide) for inhalation
INDICATION:	Diagnostic Use
SPONSOR:	INO Therapeutics 6 Route 173 Clinton, NJ 08809
PROTOCOL:	INOT22
DRUG DEVELOPMENT PHASE:	Phase 3
VERSION:	Amendment II
DOCUMENT DATE:	[redacted]
STUDY INITIATION:	
STUDY DURATION:	2 years
MEDICAL MONITOR:	James S. Baldassarre, MD Senior Director of Research & Development Phone (908) 238-6363 Fax (908) 238-6634
REGULATORY CONTACT:	Sandra Cottrell VP-Global Regulatory Affairs Mary Ellen Zamstein U.S. & Canadian Regulatory Affairs
STUDY CONTACT:	Jodee Newman, RN Project Leader Phone (908) 238-6317 Fax (908) 238-6634
GCP:	These studies will be performed in compliance with good clinical practices (GCP) guidelines. All essential documents will be archived.

2. SYNOPSIS

Sponsor: INO Therapeutics, LLC	
Name of Finished Product: INOmax® (nitric oxide) for inhalation	
Name of Active Ingredient: Nitric Oxide for Inhalation	
Protocol Number: INOT22	
Title of Study: Comparison of Supplemental Oxygen and Nitric Oxide for Inhalation Plus Oxygen in the Evaluation of the Reactivity of the Pulmonary Vasculature During Acute Pulmonary Vasodilator Testing	
Investigators: Pr. Daniel Sidi, Dr. Alain Fraisse, Dr. Federico Larraya, Dr. Jose Luis Zunzunegui, Dr. Joaquin Jose Bartrons, Prof. Dr. Rolf Berger, Dr. Alan Magee, Dr. Mary Mullen, Dr. Robyn Barst, et al. TBD	
Study Centers: Hopital Necker, Paris, France; CHU la Timone-Hopital d'enfants, Marseille, France; Hospital Materno-Infantil XII de Octubre, Madrid, Spain; Hospital Gregorio Maranon, Madrid Spain; Hospital Sant Joan de Deu, Barcelona, Spain; Beatrix Children's Hospital, Univ. Hospital Groningen, Amsterdam, Netherlands; The Royal Brompton Hospital, London, UK; Boston Children's Hospital, Boston, MA, US; Columbia Presbyterian Hosptital, New York, NY, US, et al. TBD	
Study Period: [redacted]	**Phase of development:** III
Objectives: Compare utility and side effects of oxygen versus nitric oxide for inhalation plus oxygen in determining pulmonary vasoreactivity.	
Methodology: An open, prospective, randomized, multi-center, controlled diagnostic trial.	
Number of patients planned: Enrollment will proceed until at least 25 patients per entry diagnosis and at least 150 patients have been enrolled.	
Anticipated duration of trial: 2 years	

Diagnosis and main criteria for inclusion: Patients between the ages of 4 weeks and eighteen years undergoing diagnostic right heart catheterization scheduled to include acute pulmonary vasodilation testing to assess pulmonary vasoreactivity. The expected population will be patients with:

1) Idiopathic Pulmonary Arterial Hypertension
2) Congenital heart disease with pulmonary hypertension;
3) Cardiomyopathies;

Patients who are either under general anesthesia or awake sedation will be included in this protocol. Patients will be stratified based on entry diagnosis.

Test product, dose and mode of administration: Nitric oxide for inhalation 800 ppm, administered at a dose of 80 ppm, nitric oxide for inhalation plus 100% O_2 and 100% O_2, via facemask or endotracheal tube.

Duration of treatment: 10 minutes of nitric oxide for inhalation at 80 ppm and 10 minutes of 80 ppm nitric oxide for inhalation plus 100% O_2, and 10 minutes of 100% O_2; delivered via facemask or endotracheal tube.

Criteria for evaluation:

Primary endpoint:

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

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

1) a decrease in PAPm $\geq$ 20% and no decrease in cardiac index (within 5%)

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

1) a decrease in PAPm $\geq$ 20% and no decrease in cardiac index (within 5%)

or

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

Secondary endpoints:

1) Number of patients receiving NO versus the number of patients receiving O_2 that meet response criteria, as defined above.
2) Number of patients receiving a combination of NO and O_2 versus the number of

patients receiving NO alone that meet response criteria, as defined above.

3) PVRI, PAPm and Cardiac Index readings in Room Air versus NO alone, O_2 alone and the combination of NO and O_2
4) Change in the ratio of PAPm to SAPm by treatment
5) Survival at 1 year and 3 years by response

Safety endpoints:

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

3. TABLE OF CONTENTS

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.

Reversible Pulmonary Hypertension

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

1) a decrease in PAPm $\geq$ 20% and no decrease in cardiac index (within 5%)

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

1) a decrease in PAPm $\geq$ 20% and no decrease in cardiac index (within 5%)

or

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

5. ETHICS

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

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

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

5.2 Ethical Conduct of the Study

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

5.3 Patient Information and Informed Consent

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

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

5.4 Financial Interest Statement

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

6. INVESTIGATORS AND STUDY ADMINISTRATION STRUCTURE

6.1 Investigators

Approximately 18 sites will participate in the trial with an expected total enrollment of a minimum of 150 patients (approximately 9 patients per site).

6.2 Administrative Structure

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

6.3 Steering Committee Members

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

6.4 Data Safety and Monitoring Board Members

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

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

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

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

7. INTRODUCTION

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

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

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

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

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

8. STUDY OBJECTIVES

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

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

1) a decrease in PAPm $\geq$ 20% and no decrease in cardiac index (within 5%)

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

1) a decrease in PAPm $\geq$ 20% and no decrease in cardiac index (within 5%)

or

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

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

9. INVESTIGATIONAL PLAN

9.1 Overall Study Plan and Design

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

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

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

9.2 Discussion of Study Design

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

9.3 Selection of Study Population

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

9.3.1 Inclusion Criteria

The patient must meet the following criteria:

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

c. Cardiomyopathy

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

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

9.3.2 Exclusion Criteria

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

1. Focal pulmonary infiltrates on chest radiograph.
2. Diagnosed with severe obstructive or restrictive pulmonary disease that is significantly contributing to the patient's pulmonary hypertension.
3. Received treatment with nitric oxide for inhalation within 30 days prior to study initiation, are on other investigational medications, nitroglycerin, sodium nitroprusside, sildenafil, other PDE-5 inhibitors, or prostacyclin.
4. Pregnant (urine HCG +).
5. Baseline PCWP > 20 mmHg

9.3.3 Removal of Patients from Therapy or Assessment

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

9.4 Treatments

9.4.1 Treatments Administered

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

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

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

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

9.4.2 Identity of Investigational Product

The active drug, nitric oxide for inhalation, will be manufactured by INO Therapeutics. Nitric oxide for inhalation will be supplied in size "88" US or "10L" EU, aluminum cylinders at a concentration of 800 ppm, balance nitrogen (99.92% grade 5 nitrogen, 0.08% pharmaceutical grade nitric oxide). The cylinders should be stored in a controlled, limited access area at standard room temperature. Cylinders labels will distinguish among sites but will not be pre-assigned patient numbers. The oxygen used in this study will be provided by each hospital.

9.4.3 Method of Assigning Patients to Treatment Groups

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

9.4.4 Selection of Doses in the Study

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

9.4.5 Selection and Timing of Dose for Each Patient

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

9.4.6 Treatment Group Assignment Blinding

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

9.4.7 Prior and Concomitant Therapy

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

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

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

9.4.8 Treatment Compliance

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

9.5 Efficacy and Safety Variables

9.5.1 Efficacy and Safety Schedule of Assessments

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

Table 1. Schedule of Assessments

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

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

Table 2. Schedule of Treatments

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

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

9.5.2 Data Collection

Baseline Measurements

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

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

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

Measurements Following First Treatment Administration

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

Measurements Following Second Treatment Administration

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

Measurements Following Third Treatment Administration

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

Measurements 1 year and 3 years after the diagnostic procedure

- Therapies received since the diagnostic procedure
- Date of surgery (if any)
- Vital status and date of death, if applicable

Procedures for Maintenance of Baseline Oxygen Saturation Levels

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

Awake Sedation Patients

Patients Not on Supplemental O_2

1. Right heart catheterization.
2. Place properly fitted, sealed facemask on patient (check for leaks).
3. Using 21% oxygen, adjust flow to 15 L/min.
4. Allow for a 10-minute equilibrium period.
5. Take baseline hemodynamic measurements.
6. Note patient's SpO_2 reading and analyzed O_2 reading (INOvent monitor).
7. Start treatment (80 ppm NO or 100% O_2 as per randomization table).
8. After 1 minute, adjust oxygen blender to maintain the patient's baseline analyzed O_2 reading. For the nitric oxide for inhalation treatment, expect a 10% decrease in the patient's FiO_2. During this treatment, you may adjust the blender setting by 10% so as to maintain the baseline O_2 reading.
9. Maintain treatment for 10 minutes.
10. Take hemodynamic measurements.
11. Start second treatment by adding either 80 ppm NO or 100% O_2 so that the administered treatment is a combination of 80 ppm NO and 100% O_2.
12. Maintain treatment for 10 minutes.
13. Take hemodynamic measurements.
14. Stop treatment but do not remove facemask until completion of the study.
15. Adjust oxygen blender to maintain monitored FiO_2 reading of 21%.
16. Do not remove facemask (The facemask will remain in place during the entire procedure. Although it may be loosened during the wash out periods to maintain patient comfort).
17. 10 minute wash out period.
18. Take baseline hemodynamic measurements
19. Start third treatment of either 80 ppm NO or 100% O_2. The third treatment will be whichever study gas was not administered during the first treatment period.
20. Maintain treatment for 10 minutes.

21. Take hemodynamic measurements.
22. Stop treatment.
23. Adjust oxygen blender to maintain monitored FiO_2 reading of 21%.
24. Allow for a ten-minute equilibrium period.
25. Remove facemask from patient.

Patients on Supplemental O_2

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

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

5. Re-check patient's O_2 saturation level. It should be the same as initial value, if not, adjust the blender accordingly.
6. Note analyzed O_2 reading from INOvent.
7. Allow for a 10-minute equilibrium period.
8. Take baseline hemodynamic measurements.
9. Start treatment (80 ppm NO or 100% O_2 as per randomization table).
10. After 1 minute adjust the oxygen blender to maintain the baseline SpO_2.
11. Note analyzed O_2 reading from INOvent.
12. Maintain treatment for 10 minutes.
13. Take hemodynamic measurements.
14. Start second treatment by adding either 80 ppm NO or 100% O_2 so that the administered treatment is a combination of 80 ppm NO and 100% O_2.
15. Maintain treatment for 10 minutes.
16. After 1 minute adjust the oxygen blender to maintain the baseline SpO_2.
17. Take hemodynamic measurements
18. Stop treatment but do not remove facemask until completion of study.

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

Patients Intubated and Under General Anesthesia

Patients Not on Supplemental O_2

1. Patients will be placed under general anesthesia and intubated according to the standard medical care and procedures of the institution.
2. Right heart catheterization.
3. Using 21% oxygen, adjust flow to 15 L/min.
4. Allow for a 10-minute equilibrium period.
5. Take baseline hemodynamic measurements.
6. Note patient's SpO_2 reading and analyzed O_2 reading (INOvent monitor).
7. Start treatment (80 ppm NO or 100% O_2 as per randomization table).
8. After 1 minute, adjust oxygen blender to maintain the patient's baseline analyzed O_2 reading. For the nitric oxide for inhalation treatment, expect a 10% decrease in the patient's FiO_2. During this treatment, you may adjust the blender setting by 10% so as to maintain the baseline O_2 reading.
9. Maintain treatment for 10 minutes.
10. Take hemodynamic measurements.
11. Start second treatment by adding either 80 ppm NO or 100% O_2 so that the administered treatment is a combination of 80 ppm NO and 100% O_2.

12. After 1 minute, adjust oxygen blender to maintain the patient's baseline analyzed O_2 reading.
13. Maintain treatment for 10 minutes.
14. Take hemodynamic measurements.
15. Stop treatment.
16. Adjust oxygen blender to maintain monitored FiO_2 reading of 21%.
17. 10 minute wash out period.
18. Take baseline hemodynamic measurements
19. Start third treatment of either 80 ppm NO or 100% O_2. The third treatment will be whichever study gas was not administered during the first treatment period.
20. After 1 minute, adjust oxygen blender to maintain the patient's baseline analyzed O_2 reading.
21. Maintain treatment for 10 minutes.
22. Take hemodynamic measurements.
23. Stop treatment.
24. Adjust oxygen blender to maintain monitored FiO_2 reading of 21%.
25. Extubation will occur according to each institution's standard of care.

Patients on Supplemental O_2

1. Before intubation and initiation of general anesthesia, obtain patients baseline oxygen saturation levels (pulse oximetry) with patient's supplemental oxygen in place.
2. Patients will be placed under general anesthesia and intubated according to the standard medical care and procedures of the institution.
3. Right heart catheterization
4. Adjust the patient's O_2 to match delivery they were receiving through nasal cannula prior to study enrollment.

2. Re-check patient's O_2 saturation level. It should be the same as initial value, if not, adjust the blender accordingly.
3. Note analyzed O_2 reading from INOvent.
4. Allow for a 10-minute equilibrium period.

7. Take baseline hemodynamic measurements.
8. Start first treatment (80 ppm or 100% O_2 as per randomization table).
9. After 1 minute adjust oxygen blender to maintain baseline SpO_2.

10. Maintain treatment for 10 minutes.
11. Take hemodynamic measurements.
12. Start second treatment by adding either 80 ppm NO or 100% O_2 so that the administered treatment is a combination of 80 ppm NO and 100% O_2.
13. After 1 minute adjust oxygen blender to maintain baseline SpO_2.
14. Maintain treatment for 10 minutes.
15. Take hemodynamic measurements.
16. Stop treatment.
17. Adjust oxygen blender to maintain patient's baseline SpO_2.
18. Ten minute wash out period
19. Take baseline hemodynamic measurements
20. Start third treatment of either 80 ppm NO or 100% O_2. The third treatment will be whichever study gas was not administered during the first treatment period.
21. Adjust oxygen blender to maintain patient's baseline SpO_2.
22. Maintain treatment for 10 minutes.
23. Take hemodynamic measurement.
24. Stop treatment.
25. Adjust oxygen blender to maintain patient's baseline SpO_2.
26. Allow for a ten-minute equilibrium period.
27. Extubation will occur as per each institutions standard of care.

9.5.3 Ventilator Weaning and Extubation Strategy

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

9.5.4 Appropriateness of Measurements

Demographic and baseline data will be collected and evaluated in an attempt to demonstrate that the treatment groups are well balanced with respect to age, sex, race,

and that there were no substantial differences in either population with regards to the underlying disease. The measured and calculated values in this protocol are used in standard clinical practice to assess pulmonary vasoreactivity. Both the PAPm and the PVRI have been shown to be useful parameters in measuring the body's response to vasoactive drug therapy.

9.5.5 Efficacy Variables

Primary endpoint:

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

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

1) a decrease in PAPm $\geq$ 20% and no decrease in cardiac index (within 5%)

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

1) a decrease in PAPm $\geq$ 20% and no decrease in cardiac index (within 5%)

or

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

Secondary endpoints:

1) Number of patients receiving NO versus the number of patients receiving O_2 that meet response criteria, as defined above.

2) Number of patients receiving a combination of NO and O_2 versus the number of patients receiving NO alone that meet response criteria, as defined above.

3) PVRI, PAPm and Cardiac Index readings in Room Air versus NO alone, O_2 alone and the combination of NO and O_2.

4) Change in the ratio of PAPm to SAPm by treatment

5) Survival at 1 year and 3 years, by response

9.5.6 Safety Variables

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

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

9.5.7 Drug Concentration Measurements

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

9.6 Data Quality Assurance

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

9.7 Statistical Methods Planned and Determination of the Sample Size

See Appendix 2.

9.7.1 Sample Size Determination

The following assumptions are made:

1. The desired type I (α) error of 0.05 is the threshold for statistical significance (2-tailed)

2. The expected percentage of patients who have a reduction in PVR of ≥ 20% using 80 ppm NO and 100% O_2 and will have a reduction in PVR of ≤ 20% using 100% O_2 will be 24%.[7]
3. The expected percentage of patients who have a reduction in PVR of ≥ 20% using 100% O_2 and will have a reduction in PVR of ≤ 20% using 80 ppm NO and 100% O_2 will be 0%.[7]
4. The desired power (1 - ß) for the trial is 80%.

Enrollment will proceed until at least 150 patients have been enrolled in the trial.

9.7.2 Interim Analysis

No interim analysis is planned for this trial.

9.8 Changes in Conduct of the Study or Planned Analyses

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

10. ADMINISTRATIVE DETAILS

10.1 Accountability of Study Drug and Equipment

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

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

10.2 Case Report Forms

All case report forms are to be completed within one month after patient completion of the study. A case report form is provided for each patient. All forms are to be filled out in black ink or typed.

Correction(s) of data on the case report form should be made by crossing out the incorrect data (in a manner that leaves the previous entry identifiable) and writing the correct values next to those crossed out. Each correction must be initialed and dated by the individual making the correction.

10.3 Investigator Requirements

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

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

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

10.4 Recording of Adverse Events

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

10.4.1 Study Drug Relationship

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

Not Related

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

Remote

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

Possible

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

Probable

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

Highly Probable

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

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

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

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

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

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

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

10.4.2 Serious Adverse Events

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

Catherine Evans

INO Therapeutics Regulatory Affairs Associate

Phone: +001 908 238-6655

Fax: +001 908 238-6635

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

James S. Baldassarre, MD

INO Therapeutics Senior Director of Research & Development

Phone: +001 908 238-6363

Cell: +001 908 500-8111

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

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

10.4.3 Unexpected Adverse Events

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

10.5 Records Retention

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

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

10.6 Monitoring and Audits

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

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

10.7 Amendments to the Protocol

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

10.8 Termination of Trial

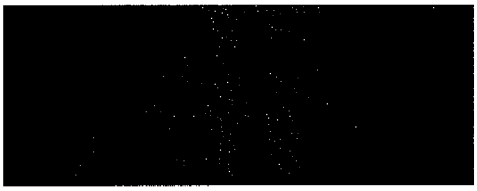
It is agreed that, for reasonable cause, either the investigator or the sponsor, INO Therapeutics, LLC may terminate this study, provided written notice is submitted at a reasonable time in advance of intended termination.

11. REFERENCE LIST

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

APPENDIX 1. PROTOCOL VERSIONS

Protocol Versions:



APPENDIX 2. ANALYTIC PLAN

A. Analysis Populations

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

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

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

B. Analyses of Baseline Characteristics

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

C. Primary Efficacy Analysis

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

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

1) a decrease in PAPm $\geq$ 20% and no decrease in cardiac index (within 5%)

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

1) a decrease in PAPm $\geq$ 20% and no decrease in cardiac index (within 5%)

or

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

These variables will be calculated as follows:

% Change in PAPm from Baseline =

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

% Change in PVRI from Baseline =

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

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

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

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

The alternative hypothesis is:

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

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

D. Secondary Efficacy Analysis

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

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

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

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

The alternative hypothesis is:

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

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

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

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

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

The alternative hypothesis is:

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

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

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

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

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

The alternative hypothesis is:

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

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

The alternative hypothesis is:

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

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

The alternative hypothesis is:

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

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

The alternative hypothesis is:

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

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

The alternative hypothesis is:

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

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

The alternative hypothesis is:

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

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

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

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

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

Change in the Ratio of PA Pressure to Systemic Pressure

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

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

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

Survival at 1 and 3 Years Following the Diagnostic Procedure

It is hypothesized that there is a difference in rates of survival at 1 and 3 years of those who met response criteria as outlined in section C of this analytic plan. The hypotheses are formerly expressed as:

H_o: There is no difference in the survival rate of patients with a positive response in PAPm or PVRI between the NO and O_2 group versus the O_2 alone group.
The alternative hypothesis is:
H_a: A difference exists in the survival rate of patients with a positive response in PAPm or PVRI between the NO and O_2 group versus the O_2 alone group.

The difference between the two treatment groups will be tested using the Fisher's Exact Test. This test will be conducted with the type I (α) error of 0.05 for statistical significance (2-tailed). In addition, a Kaplan-Meier plots will be generated for time to death for each treatment group.

E. Safety Analysis

Serious Adverse Events

The analysis will be performed on the number and types of serious adverse events reported in each treatment group. The incidence of all serious adverse events, stratified by MEDRA terms, MEDRA body system, and patients with specific serious adverse events will be tabulated. Additionally, the serious adverse events will be stratified by age, sex and race.

H_o: There is no difference in the number of reported serious adverse events between the NO, NO + O_2 and O_2 alone groups.

H_a: A difference exists in the number of reported serious adverse events between the NO, NO + O_2 and O_2 alone groups.

This comparison will be made using Cochran's Test for Related Observations.

Drug Related Adverse Events

The analysis will be performed on the number and types of drug related adverse events reported in each treatment group. The incidence of all drug related adverse events, stratified by MEDRA terms, MEDRA body system, and patients with specific adverse events will be tabulated. Additionally, the adverse events will be stratified by age, sex and race.

H_o: There is no difference in the number of reported drug related adverse events between the NO, NO + O_2 and O_2 alone groups.

H_a: A difference exists in the number of reported drug related adverse events between the NO, NO + O_2 and O_2 alone groups.

This comparison will be made using Cochran's Test for Related Observations.

F. Additional Analyses

All primary methods of analysis have been previously outlined in this document. However, INO Therapeutics reserves the right to perform any additional analyses deemed necessary according to any of the following reasons:

1. Any steering committee or medical monitor recommendations based on investigator concerns.
2. The presence of maldistributed baseline characteristics.
3. The administration of any medications thought to be affecting the treatment as determined by the steering committee and/or the medical monitor.

Additionally, several exploratory analyses will be conducted to determine the existence of any possible relationships between the response variables and diagnosis, delivery system, demographic criteria, etc. Due to the unknown nature of these analyses, INO Therapeutics, LLC declines to formalize the testing procedures in this analytic plan.

G. Interim Analyses

No interim analysis for efficacy or safety in this study is planned.

APPENDIX 3. LISTING OF AMENDMENT 1 CHANGES

AMENDMENT 1 CHANGES:

Cover Page, Version

Changed From:

"Original Protocol"

Changed To:

"Amendment 1"

Cover Page, Document Date

Changed From:

[redacted]

Changed To:

[redacted]

Cover Page, Study Contact

Deleted: Paul Bridges, European Regulatory Affairs

Changed From:

"Rebecca Light, Clinical Research Manager"

Changed To:

"Jodee Newman, Project Leader"

Synopsis

Changed From:
"Sponsor-INO Therapeutics, Inc."

Changed To:
"Sponsor-INO Therapeutics, LLC"

Changed From:
"Investigators-TBD"

Changed To:
"Investigators- Pr. Daniel Sidi,, Dr. Alain Fraisse, Dr. Federico Larraya, Dr. Jose Luis Zunzunegui, Dr. Joaquin Jose Bartrons, Prof. Dr. Rolf Berger, Dr. Alan Magee, Dr. Mary Mullen, Dr. Robyn Barst "

Changed From:
"Study Centers-TBD"

Changed To:
Study Centers-Hopital Necker, Paris, France; CHU la Timone-Hopital d'enfants, Marseille, France; Hospital Materno-Infantil XII de Octubre, Madrid, Spain; Hospital Gregorio Maranon, Madrid Spain; Hospital Sant Joan de Deu, Barcelona, Spain; Beatrix Children's Hospital, Univ. Hospital Groningen, Amsterdam, Netherlands; The Royal Brompton Hospital, London, UK; Boston Children's Hospital, Boston, MA, US; Columbia Presbyterian Hosptital, New York, NY, US

Secondary Endpoints-Addition:

4) Change in the ratio of PAPm to SAPm by treatment

5) Survival at 1 year by response

4. List of Abbreviations and Definitions of Terms

Addition:
Mean Systolic Arterial blood pressure

Page 19 Section 9.1

Addition:
"Following the acute diagnostic procedure, a brief follow up contact will be made on each patient to determine the vital status 1 year after the diagnostic procedure."

Section 9.5.1 Table 1 - Footnote

Addition:
Assessment-Baseline :Arterial pH
Follow up assessment at 1 yr. Will consist of telephone call to assess medical therapies or surgical procedures pertaining to pulmonary/cardiac disease, and vital status /date of death if applicable.

9.5.2 Data Collection

Addition:
Of Arterial pH to-

Baseline Measurement ***and*** *Measurements Following Third Treatment Administration*

Measurements 1 year after the diagnostic procedure

- Therapies received since the diagnostic procedure
- Date of surgery (if any)
- Vital status and date of death, if applicable

9.5.5 Efficacy Variables

Secondary Endpoints-Addition:

4) Change in the ratio of PAPm to SAPm by treatment

5) Survival at 1 year by response

10.4.2 Serious Adverse Events

Changed From:

Any serious adverse event must be reported to INO Therapeutics within 24 hours by telephone to:

Catherine Evans, Regulatory Affairs Associate

Phone: (908) 238-6655

Fax: (908) 238-6635

Dr. James S. Baldassarre

Phone: (908) 238-6363 Cell: (908) 500-8111

Changed To:

All serious adverse events occurring during the study, and within 12 hours of the discontinuation of treatment gas, or hospital discharge whichever comes first, must be reported within 24 hours to INO Therapeutics by fax/telephone to:

Catherine Evans

INO Therapeutics Regulatory Affairs Associate

Phone: + 001 908 238-6655

Fax: +001 908 238-6635

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

Dr. James S. Baldassarre

INO Therapeutics Senior Director Research & Development

Phone: +001 908 238-6363

Cell: +001 908 500-8111

Added to text: *"within 24 hours by completing an SAE packet with"*

Delete page 40, second to last paragraph:

All patient/subject deaths will be reported independent of the temporal relationship to the patient's/subject's study participation and treatment (i.e. test drug, placebo).

Appendix 2. Analytic Plan

Section D-page 46/47 Addition:

Change in the Ratio of PA Pressure to Systemic Pressure

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

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

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

Survival at 1 Year Following the Diagnostic Procedure

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

H_o: There is no difference in the survival rate of patients with a positive response in PAPm or PVRI between the NO and O_2 group versus the O_2 alone group.
The alternative hypothesis is:
H_a: A difference exists in the survival rate of patients with a positive response in PAPm or PVRI between the NO and O_2 group versus the O_2 alone group.

The difference between the two treatment groups will be tested using the Fisher's Exact Test. This test will be conducted with the type I (α) error of 0.05 for statistical significance (2-tailed). In addition, a Kaplan-Meier plots will be generated for time to death for each treatment group.

APPENDIX 4. LISTING OF AMENDMENT II CHANGES

AMENDMENT II CHANGES:

Cover Page, Version

Changed From:

"Amendment I"

Changed To:

"Amendment II"

Cover Page, Document Date

Changed From:

[redacted]

Changed To:

[redacted]

Cover Page, Duration

Changed From:

"1 ½ years"

Changed To:

"2 years"

Cover Page, Study Contact

Addition:

Sandra Cottrell
VP Global Regulatory Affairs

Synopsis

Investigators

Addition:
et al. TBD

Study Centers

Addition:
et al. TBD

Study Period

Anticipated Completion:

Changed From:

[redacted]

Changed To:

[redacted]

Anticipated duration of trial

Changed From:

1½ years

Changed To:

2 years

Criteria for Evaluation

Secondary Endpoints:

Changed From:

5) Survival at 1 year by response

Changed To:

5) Survival at 1 year and 3 years by response

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

Changed To:
Approximately 18 sites will participate in the trial with an expected total enrollment of a minimum of 150 patients (approximately 9 patients per site).

9.3.2Exlusion Criteria

Addition:

5) Baseline PCWP > 20 mmHg

9.4.2 Identity of Investigational Product

Changed From:
Nitric oxide for inhalation will be supplied in size "88", aluminum cylinders at a concentration of 800 ppm, balance nitrogen (99.92% grade 5 nitrogen, 0.08% pharmaceutical grade nitric oxide).

Changed To:

Nitric oxide for inhalation will be supplied in size "88" US or "10L" EU, aluminum cylinders at a concentration of 800 ppm, balance nitrogen (99.92% grade 5 nitrogen, 0.08% pharmaceutical grade nitric oxide).

9.5 Table 1

Addition to table:

pH- following third treatment administration

Addition to Footnote:

3 year follow up

9.5.2 Data Collection

Changed From:

Measurements 1 year after the diagnostic procedure

Changed To:

Measurements 1 year and 3 years after the diagnostic procedure

9.5.5 Efficacy Variables

Secondary Endpoints

Changed From:

Survival at 1 year by response

Changed To:

Survival at 1 year and 3 years, by response

9.7.1 Sample Size Determination

Changed From:

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

Changed To:

Enrollment will proceed until at least 150 patients have been enrolled in the trial.

Throughout document:

Changed From:

INO Therapeutics, Inc.

Changed To:

INO Therapeutics, LLC

Appendix 2. Analytic Plan -D. Secondary Efficacy Analysis

Changed From:

Survival at 1 Year Following the Diagnostic Procedure

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

Survival at 1 and 3 Years Following the Diagnostic Procedure

It is hypothesized that there is a difference in rates of survival at 1 and 3 years of those who met response criteria as outlined in section C of this analytic plan.

Appendix 3. Amendment I Changes

Section 9.1

Changed From:

Page 14

Changed To:

Page 19

Appendix 2. Analytic Plan Section D

Changed From:

Page 42/43

Changed To:

Page 46/47

Secondary Endpoints:

Point #5 corrected from #6.

INVESTIGATOR AGREEMENT

Protocol INOT22
Version: Amendment II

I have read the protocol, "Comparison of Supplemental Oxygen and Nitric Oxide for Inhalation Plus Oxygen in the Evaluation of the Reactivity of the Pulmonary Vasculature During Acute Pulmonary Vasodilator Testing", Protocol INOT22 (version 1), and agree to conduct the study as outlined therein. I will make a reasonable effort to conduct the study in a timely and efficient manner and will ensure that all participating staff members are adequately trained to carry out the tasks for which they have been assigned.

I will submit this protocol and all other pertinent information to my IRB/IEC for approval.

_____ _____
Principal Investigator's Signature Date

_____
Name of investigator (printed)

6 Route 173, Clinton, NJ 08809
Tel (908) 238-6600 Fax (908) 238-6633
http://www.inotherapeutics.com

[redacted]

Center for Drug Evaluation and Research
Office for Drug Evaluation I
Division of Cardio-Renal Drug Products
(HFD-110)
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

IND 63,096
INOmax® (nitric oxide) for inhalation

Serial No.: 091

Protocol Amendment
Change in Protocol
New Investigator: Updated Investigator Information

Dear Sir or Madam:

Reference is made to Investigational New Drug Application 63,096 for the treatment of cardiopulmonary disease and sickle cell disease. At this time we wish to provide amendments to protocols INOT22 and INOT43. Also, we wish to provide new investigator information and an amendment to protocol INOT41 and new investigator information for INOT36.

Protocol INOT22
Comparison of Supplemental Oxygen and Nitric Oxide for Inhalation Plus Oxygenation in the Evaluation of the Reactivity of the Pulmonary Vasculature During Acute Pulmonary Vasodilator Testing. (Originally submitted [redacted] Serial No. 071 and amended [redacted] Serial No. 083)

Below is a list of major changes incorporated into protocol INOT22, Amendment 2.

- Anticipated duration of trial changed from 1 ½ to 2 years.
- Revised investigator sites information from approximately 8 sites with approximately 20 patients per site to approximately 18 sites with approximately 9 patients per site.
- Revised exclusion criteria to add Baseline PCWP> 20 mmHg.
- Revised data collection from 1 year after the diagnostic procedure to 1 year and 3 years after the diagnostic procedure.
- Revised sample size determination from "the minimum number of patients required per entry diagnosis is 25. Enrollment will proceed until at least 25 patients per entry

diagnosis are enrolled and there are at least 150 patients in the trial" to "Enrollment will proceed until at least 150 patients have been enrolled in the trial."

- Appendix 2. Analytic Plan –D. Secondary Efficacy Analysis changed from 1 year to 1 and 3 years.

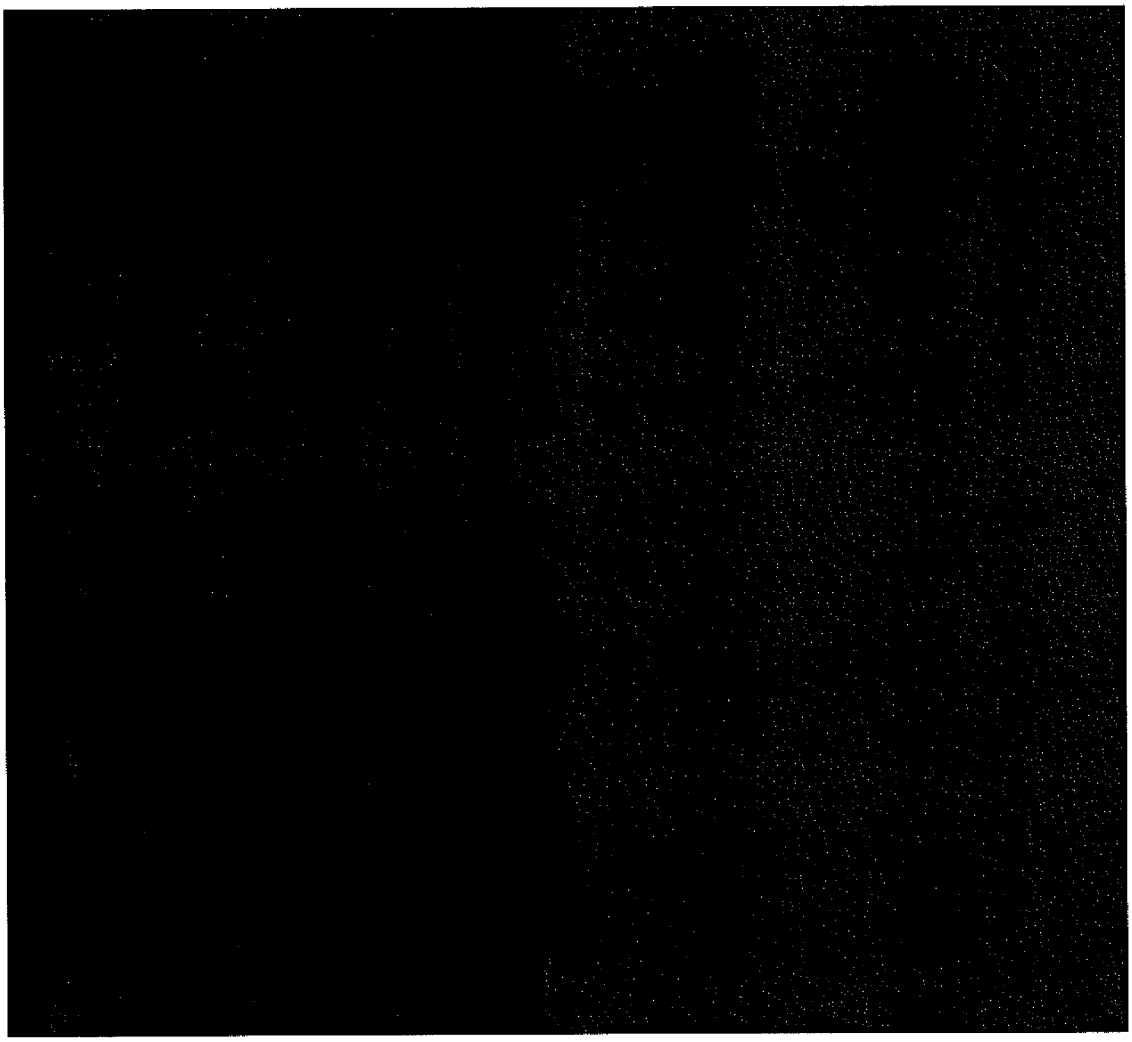
For ease of review, a detailed list of all revisions to this amended protocol is included in appendix 4 of the appended protocol.

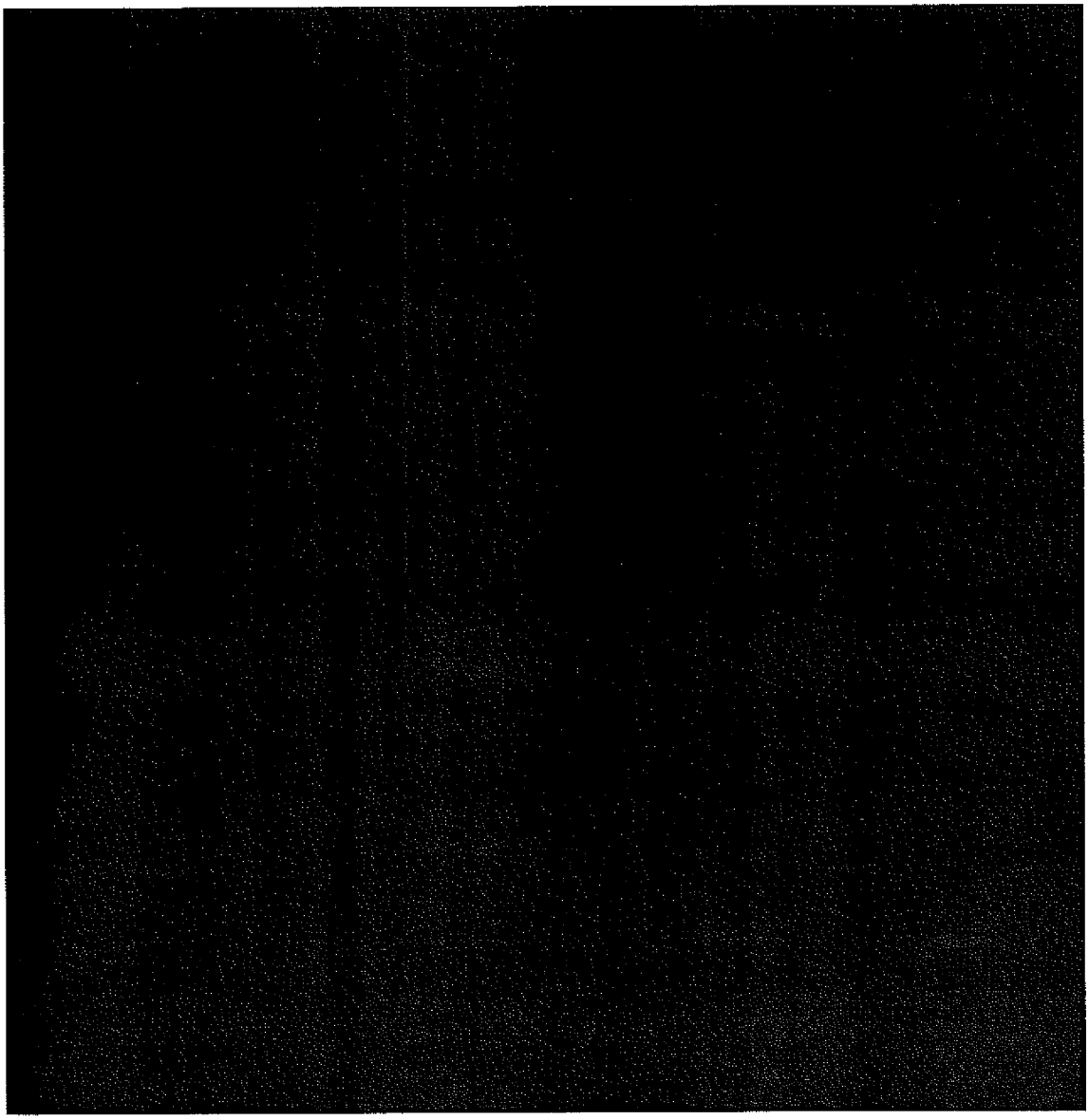
Prior to enrollment of subjects under Amendment 2, further revisions were made to the protocol resulting in Amendment 3.

Below is a list of major changes incorporated into protocol INOT22, Amendment 3.

- Revised sample size information from 150 patients to 100 patients.

For ease of review, a detailed list of all revisions to this amended protocol is included in appendix 5 of the appended protocol.





Should you have any questions and/or comments, please contact me directly at 908-238-6337.

Sincerely,

INO Therapeutics,

Mary Ellen Zamstein

Mary Ellen Zamstein
Director, Regulatory Affairs

F: Regulatory IND 63,096 Protocol Amendments [redacted] FDA letter.doc

APPENDIX 5

[redacted]

From: Debra A. Rimar
Sent: [redacted]
To: James Baldassarre
Subject: FW: INOT22 - latest draft CSR (v.0.3)

Sorry.

Debra Rimar
INO Therapeutics/IKARIA
6 Route 173
Clinton, NJ 08809
debra.rimar@ikaria.com
908.238.6322

From: James Baldassarre
Sent: [redacted]
To: Debra A. Rimar
Subject: RE: INOT22 - latest draft CSR (v.0.3)

There's no attachment.

jim

From: Debra A. Rimar
Sent: [redacted]
To: James Baldassarre
Subject: INOT22 - latest draft CSR (v.0.3)
Importance: High

Jim:

Latest version w/inclusion of two recent tables + new pvri Figure 5 + various minor changes.

See highlighted areas needing possible attention.

Jodee taking Safety section.

Make changes directly in the doct. and return and I will merge into master.

Debra Rimar
INO Therapeutics/IKARIA
6 Route 173

Clinton, NJ 08809
debra.rimar@ikaria.com
908.238.6322

NITRIC OXIDE FOR INHALATION, INOmax®

INOT22

COMPARISON OF SUPPLEMENTAL OXYGEN AND NITRIC OXIDE FOR INHALATION PLUS OXYGEN IN THE EVALUATION OF THE REACTIVITY OF THE PULMONARY VASCULATURE DURING ACUTE PULMONARY VASODILATOR TESTING

Indication studied:	*Diagnostic use*
Developmental phase of study:	*PHASE 3*
First patient enrolled:	*<<Date>>*
Last patient completed:	*<<Date>>*
Release date of report:	*<<Date>>*

Company/Sponsor signatory: *<<Name>>*
<<Telephone Number>>
<<Fax Number>>

This trial was conducted in accordance with the ethical principles of Good Clinical Practice (GCP), according to the International Conference on Harmonisation (ICH) Harmonized Tripartite Guideline.

Sponsor's Responsible Medical Officer <<Signature, Date>>

3. TABLE OF CONTENTS FOR THE INDIVIDUAL CLINICAL STUDY REPORT

TABLE OF CONTENTS

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LIST OF FIGURES

4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and specialist terms are used in this study report.

Table 1: Abbreviations and Specialist Terms

Abbreviation or specialist term	Explanation
AE	Adverse event
APVT	Acute pulmonary vasodilator testing
CFR	Code of federal regulations
CHD	Congenital heart disease
CI	Cardiac index
CO	Cardiac output
CRA	Clinical research associate
CRF	Case report form
CVPm	Mean central venous pressure
DAP	Diastolic arterial blood pressure
FDA	Food and Drug Administration
GCP	Good Clinical Practice
Hgb	Hemoglobin
HR	Heart rate
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IPAH	Idiopathic pulmonary hypertension
IRB	Institutional Review Board
MAP	Mean arterial pressure
mm Hg	Millimeters of mercury
n	Total number of patients (sample size)
NO	Nitric oxide
NO_2	Nitrogen dioxide
O_2	Oxygen
PAP	Pulmonary arterial pressure

Abbreviation or specialist term	Explanation
PAPm	Mean pulmonary arterial pressure
PAPs	Systolic pulmonary arterial pressure
PAWPm	Mean pulmonary artery wedge pressure
PCWP	Pulmonary capillary wedge pressure
PDE5	Phosphodiesterase type 5
PH	Pulmonary hypertension
ppm	Parts per million by volume (40 pm = 0.004% of the inhaled gas)
PVR	Pulmonary vascular resistance
PVRI	Pulmonary vascular resistance index
SAE	Serious adverse event
SAP	Systolic arterial blood pressure
SAPm	Mean systolic arterial blood pressure

5. ETHICS

5.1. Independent Ethics Committee (IEC) or Institutional Review Board (IRB)

The protocols and local Informed Consent Forms were reviewed and approved by each of the participating institution's IRB/IEC prior to the initiation of patient accrual. The IRB/IEC was notified of all protocol amendments. In addition, progress reports were submitted to the IRB/IEC by the investigator as indicated by the IRB/IEC's guidelines. Each IRB/IEC met the Food and Drug Administration's (FDA) and/or International Conference on Harmonization (ICH) requirements for composition, documentation, and operational procedures. A list of all IECs and IRBs is provided in Appendix 16.1.3 along with the name of the committee chair.

5.2. Ethical Conduct of the Study

This trial was designed and monitored in accordance with INO Therapeutics LLC procedures, which comply with the ethical principles of Good Clinical Practices (GCP) as required by the major regulatory authorities, and in accordance with the Declaration of Helsinki.

5.3. Patient Information and Consent

All patients (or legally authorized representative) provided informed written consent after having had adequate time to consider their participation in the study. Consent was obtained prior to any protocol-related procedures that were not part of the patient's normal care. Written documentation of consent was recorded on a signature page and the patient or their legal representative received a copy of the consent form according to ICH GCP guidelines. A sample of the consent form is provided in Appendix 16.1.3.

6. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

A total of 19 sites participated in the trial with a total enrollment of 136 patients. A listing of principal investigators at each study site and their institutional affiliations is provided in Appendix 16.1.4. Signatures of principal investigators are provided in Appendix 16.1.5.

The study was initiated by INO Therapeutics LLC and a Steering Committee was established to review the contents of the protocol and subsequent amendments, monitor the progress of the trial, and provide recommendations to the sponsors on changes in the procedures and conduct of the trial. Steering Committee members included:

- David Wessel, MD, Boston Children's Hospital, Boston, MA, USA.
- Robyn Barst, MD, Columbia Presbyterian Hospital, New York, NY, USA.
- Duncan Macrae, MD, Royal Brompton Hospital, London, UK.

Due to the short duration of the study, the fact that the treatment assignments were not blinded and the fact that the study endpoints were not serious irreversible events, no Data Safety Monitoring Board was established and no interim analysis of efficacy was carried out. To ensure the well-being of patients enrolled in the trial, safety was monitored on an ongoing basis. All adverse events (AEs) and serious AEs (SAEs) were reviewed by the Steering Committee on a regular basis and reported to the appropriate health authorities and IRBs/IECs as per ICH GCP and as required by local regulations.

7. INTRODUCTION

Pulmonary hypertension (PH) is a condition characterized by elevated pulmonary artery pressures. Pulmonary hypertension may be idiopathic (i.e., without an identified cause) or secondary to other disease processes (e.g., intrinsic heart or lung disease, collagen-vascular disease, toxins or infections).[1,2] In either case, it is associated with changes in the pulmonary vascular bed such as vasoconstriction, vascular-wall remodeling, and thrombosis *in situ* resulting in increased vascular resistance.[2] Abnormal production of vasorelaxants and vasoconstrictors by the pulmonary endothelium may also play a role. Endothelium-derived metabolite imbalances of the vasorelaxant prostacyclin and vasoconstrictor thromboxane have been linked to PH, as have impaired synthesis of the vasorelaxant nitric oxide (NO) and enhanced production of vasoconstrictor endothelin.[2-5] Conventional medical treatments consisting of vasodilators, inotropes, anticoagulants, diuretics or oxygen (O_2) are aimed at decreasing mean pulmonary arterial pressure (PAPm) and pulmonary vascular resistance (PVR). In patients with primary PH and symptomatic right ventricular failure, the median survival time is less than 3 years, and surgical intervention such as heart or heart/lung transplantation may have to be considered.[2,6]

For patients with right ventricular failure and lung disorders, the prognosis and course of treatment are determined by acute pulmonary vasodilation testing (APVT). A reduction in PAPm and PVR with acute vasodilator treatment may be used to predict therapeutic efficacy of long-term vasodilator medication. APVT is also used to evaluate patients being considered for heart or heart/lung transplantation; elevated pulmonary artery pressures and PVR place a strain on the right ventricle, leading to an increased risk of perioperative morbidity and mortality due to right heart failure post-heart transplant.[7-10]

Administration of 100% supplemental O_2 has been a standard in APVT, especially in pediatric patients. However, some patients with reactive pulmonary vasculature fail to respond to acute treatment with 100% supplemental O_2. Nitric oxide has been shown to be selective for the pulmonary versus the systemic vasculature, and it does not increase pulmonary shunting.[11] It has been shown that combination testing with inhaled NO and O_2 provides additional pulmonary vasodilation in patients with a reactive vascular bed, and NO plus O_2 is more effective than O_2 alone when used as a pulmonary vasodilator.[10,11]

INOmax® (Nitric oxide for inhalation) is approved by the FDA for use in term newborns with PH and hypoxic respiratory failure in conjunction with mechanical ventilation and other supportive measures to allow more blood to circulate in the lung, which helps to increase blood O_2 levels.[12] Nitric oxide, the endothelial-derived relaxing factor, is a major physiologic regulator of endothelial smooth muscle tone. In published studies, NO for inhalation has been shown to reduce pulmonary artery pressures in patients with adult respiratory distress syndrome, chronic obstructive lung disease, PH, and congenital heart disease (CHD).[7,8,10,13] Studies in primary and secondary forms of PH have shown that short-term NO for inhalation can selectively reduce both PAPm and PVR with minimal side effects.[7,10] Nitric oxide for inhalation has a short half-life, as it quickly binds to hemoglobin (Hgb) within the pulmonary capillary lumen to form methemoglobin,

rendering it inactive, and systemic vasodilation effects with NO are minimal. Potential risks of NO are rebound PH, increased nitrogen dioxide (NO_2, a lung irritant), and methemoglobinemia. However, due to the short duration of NO delivery in this study, it is unlikely these events would occur.

This study tests the hypothesis that a combination of inhaled NO and O_2 is more sensitive than 100% supplemental O_2 alone in detecting pulmonary vasoreactivity in patients with PH.

This report is intended to report only the primary endpoint and other short-term endpoints. The results of 1- and 3-year follow-up will be reported in subsequent reports, as data becomes available.

8. STUDY OBJECTIVES

The primary objective of the trial was to compare the number of patients with reversible PH (vasoreactivity) due to NO for inhalation and O_2 as compared to 100% O_2. The criteria for response were:

- Patients with idiopathic pulmonary arterial hypertension (IPAH) or patients with CHD who did not have an unrestricted shunt at the level of the ventricle or ductus arteriosus: a decrease in PAPm ≥ 20% and no decrease in cardiac index (CI) (within 5%).
- Patients with cardiomyopathy or patients with CHD who had an unrestricted shunt at the level of the ventricle or ductus arteriosus: a decrease in PAPm ≥ 20% and no decrease in CI (within 5%) or a decrease in PVR index (PVRI) ≥ 25% and no decrease in CI (within 5%).

Additional study objectives were to compare the incidence and types of drug-related AEs and SAEs, as well as the number of patients with reversible PH due to NO for inhalation alone compared to 100% O_2 and to O_2 with NO for inhalation.

9. INVESTIGATIONAL PLAN

9.1. Overall Study Design and Plan: Description

This trial followed an open, prospective, multicenter, randomized controlled design and compared the utility and side effects of O_2, NO, and the combination of NO and O_2 in determining pulmonary reactivity. Each patient was screened for enrollment and fulfilled all entry criteria described in Section 9.3. Upon obtaining informed consent approved by the institution's IRB/IEC, patients were randomly assigned, using a randomization table, to receive either NO for inhalation at 80 parts per million (ppm) or 100% O_2 as their initial dose. Patients were either under general anesthesia or awake sedation. Once the study drug delivery equipment was prepared, baseline data were collected. Using a calibrated INOvent®, either NO for inhalation at 80 ppm or 100% O_2 was continuously administered to the patient for 10 minutes followed by data collection. The second dose was the same as the first dose with the addition of either 80 ppm NO for patients receiving O_2, or 100% O_2 for patients receiving NO. This dose of 80 ppm NO and 100% O_2 was delivered for 10 minutes followed by data collection. There was a 10 minute washout period following this administration. Baseline data were again collected followed by a 10 minute administration of either 80 ppm NO or 100% O_2. The study drug delivered for this third administration was not randomly assigned for the initial study drug administration.

For each patient, NO_2 levels were monitored throughout the treatment period. Treatment with study gas was discontinued if NO_2 levels exceeded 3 ppm. Treatment could also be discontinued at the discretion of the attending physician or following the occurrence of an adverse response to study drug. All AEs were recorded while on study gas. Serious AEs were recorded during the treatment period through Day 1 or discharge from the hospital, whichever came first. Qualification and reporting of all SAEs was carried out as per the Code of Federal Regulations (CFR) and ICH guidelines.

Following the acute diagnostic procedure, a brief follow-up contact was to be made for each patient to determine vital status 1 and 3 years after the study procedure.

9.2. Discussion of the Study Design, Including the Choice of Control Groups

This was an open, randomized, prospective, multicenter, controlled trial designed to demonstrate which diagnostic treatment was most capable of identifying patients with a reactive pulmonary vascular bed. Each patient served as his or her own control and received all three treatment regimens: 80 ppm NO for inhalation, 80 ppm NO and 100% O_2, and the comparison treatment, 100% O_2. Due to the short half-life of NO, a 10 minute washout period following the NO for inhalation and 100% O_2 treatment allowed sufficient time for elimination of the drug effect before administration of the comparison treatment. Only a single study phase without O_2 was included in this trial. This approach

was taken because an additional treatment period without O_2 would have been potentially unsafe for the unstable patients included in this study.

9.3. Selection of Study Population

The patients enrolled in this study had IPAH, CHD (with or without intravascular shunt) with PH, and cardiomyopathies. Patients were stratified based on entry diagnosis and included those who were awake or under general anesthesia. However, after the first 45 patients were enrolled, the protocol was amended such that patients with PCWP > 20 mm Hg were excluded. This was done at the suggestion of the Steering Committee due to the potential risk in that subgroup. The total sample size was reduced from 150 to 100 patients.

9.3.1. Inclusion Criteria

For inclusion into the trial, patients were required to fulfill all of the following criteria:

- Male or female 4 weeks to 18 years of age (inclusive)

  Idiopathic Pulmonary Arterial Hypertension (PAPm >25 mm Hg at rest, pulmonary capillary wedge pressure [PCWP] ≤ 15 mm Hg, and PVRI > 3W u·m^2, or diagnosed clinically with no previous catheterization)
- Congenital heart disease with PH repaired and unrepaired with PAPm > 25 mm Hg at rest, PVRI >3 Wu·m^2, or diagnosed clinically with no previous catheterization
- Scheduled to undergo right heart catheterization to assess pulmonary vasoreactivity by acute pulmonary vasodilation testing
- Signed IRB/IEC approved consent (an assent if applicable)

9.3.2. Exclusion Criteria

Any of the following was regarded as a criterion for exclusion from the trial:

- Focal pulmonary infiltrates on chest radiograph
- PWCP >20 mm Hg
- Diagnosed with severe obstructive or restrictive pulmonary disease that was significantly contributing to the patient's PH
- Received treatment with NO for inhalation within 30 days prior to study initiation, were on other investigational medications, nitroglycerin, sodium nitroprusside, sildenafil, other phosphodiesterase type 5 (PDE5) inhibitors, or prostacyclin
- Were pregnant (positive urine pregnancy test)

9.3.3. Removal of Patients from Therapy or Assessment

Patients were removed from the trial if any of the following circumstances occurred:

- Study gas was discontinued if NO_2 levels exceeded 3 ppm
- Treatment could also be discontinued if the patient or legal representative withdrew consent or if the investigator deemed it in the best medical interest of the patient

9.4. Treatments

9.4.1. Treatments Administered

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

Patients who were under general anesthesia were intubated and received NO for inhalation, 100% O_2, or a combination of NO and O_2. NO was administered using an INOvent® delivery system through a t-connector downstream of the inspiratory limb of a mechanical ventilator. Patients who were under awake sedation (mild sedation) received NO for inhalation, 100% O_2, or a combination of NO and O_2. The NO was administered using an INOvent® delivery system through a properly fitted, sealed facemask.

Each patient was randomized as to which study drug (80 ppm NO or 100% O_2) they received as the initial dose. The second dose administration was 80 ppm NO for inhalation with 100% O_2 (set - approximate O_2 delivery 90%) and the third dose administration was whichever study drug was not initially administered (NO or 100% O_2). There was a 10 minute washout period between the second and third dose administrations.

9.4.2. Identity of Investigational Products

The active drug, NO for inhalation, was manufactured by INO Therapeutics LLC. Nitric oxide for inhalation was supplied in size "88" US or "10 L" EU aluminum cylinders at a concentration of 800 ppm, balance nitrogen (99.92% grade 5 nitrogen, 0.08% pharmaceutical grade NO). The cylinders were stored in a controlled, limited access area at standard room temperature. Cylinder labels distinguished among sites, but were not pre-assigned patient numbers. The O_2 used in this study was provided by each hospital.

9.4.3. Method of Assigning Patients to Treatment Groups

Randomization of the initial study treatment administered was block randomization by site. Only the first treatment assignment was randomized. The randomization codes were provided to sites in individual envelopes per patient. Patients served as their own controls and received all three treatments.

9.4.4. Selection of Doses in the Study

While varying doses of NO for inhalation have been shown to be safe and effective in decreasing PAPm and PVRI, the use of 80 ppm may elicit a response in a small percentage of nonresponders to lower doses (Wessel D, personal communication, [redacted]). Therefore, 80 ppm of NO for inhalation was used in an effort to capture data from the maximum number of potential responders. Previous studies with NO for inhalation have shown no significant increase in the levels of methemoglobin after very short exposures, even at the dose of 80 ppm.[10,13]

9.4.5. Selection and Timing of Dose for Each Patient

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

9.4.6. Blinding

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

9.4.7. Prior and Concomitant Therapy

Patients who had received treatment with NO for inhalation within 30 days prior to study initiation, other investigational medications, nitroglycerin, sodium nitroprusside, sildenafil or other PDE5 inhibitors, or prostacyclin were excluded from this trial.

Ketamine was not to be used as part of the anesthetic regimen.

Concomitant medications were recorded on the case report form (CRF).

9.4.8. Treatment Compliance

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

9.4.9. Ventilator Weaning and Extubation Strategy

Following the third treatment administration, study patients under general anesthesia were weaned from the mechanical ventilator and extubated according to standard medical care and hospital specific protocol. Study patients under awake sedation had treatments

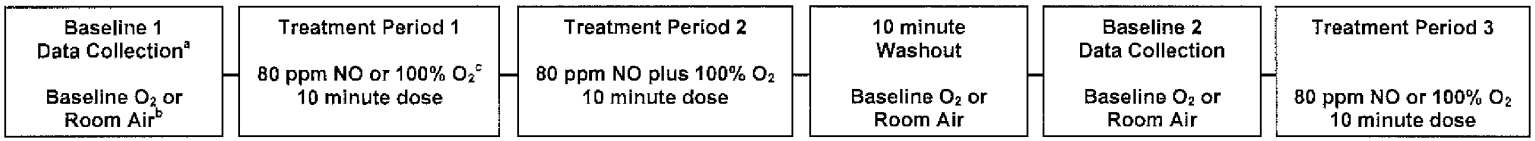
discontinued and the facemask removed according to standard medical care and hospital specific protocol.

9.5. Efficacy and Safety Variables

9.5.1. Efficacy and Safety Measurements Assessed and Flow Chart

The schedule of assessments is shown in Figure 1 and Table 2. All study procedures were carried out on a single day.

Figure 1: Study Design and Schedule Of Assessments



[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

567

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

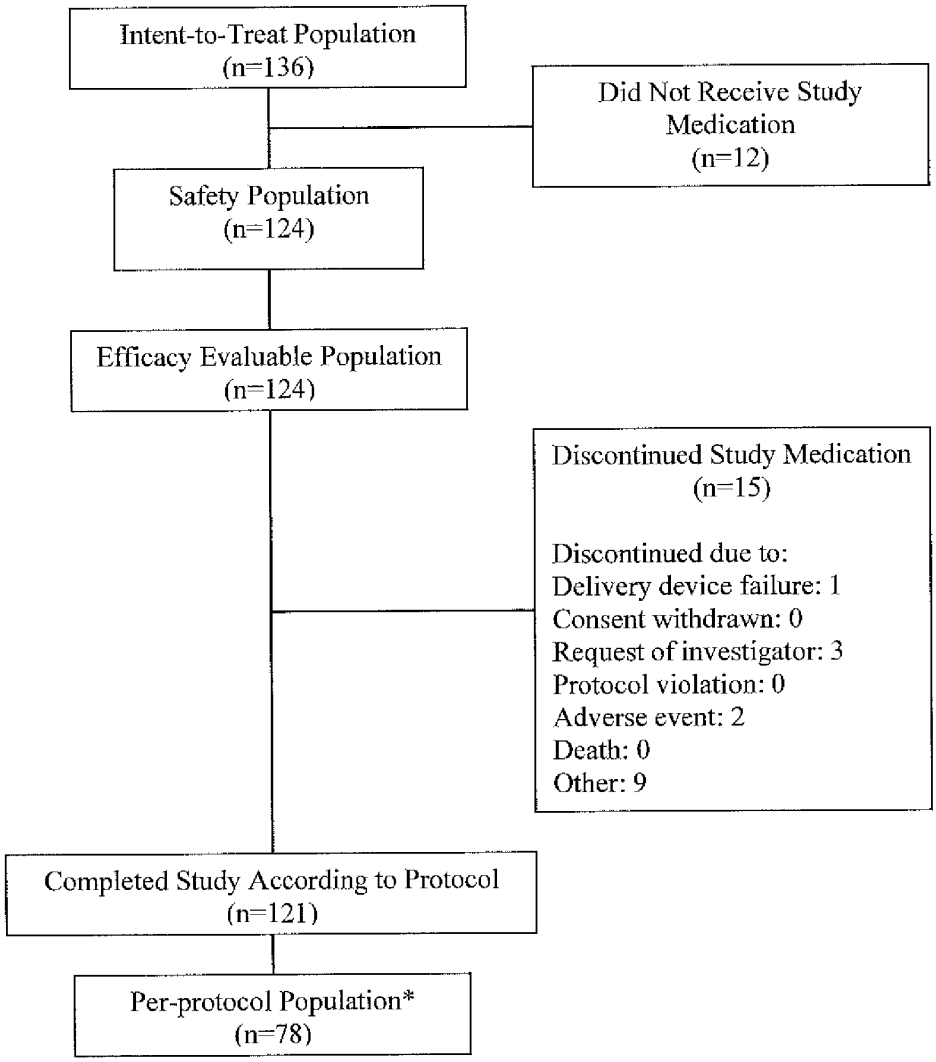
There were no significant changes in the planned conduct of the study or in any analyses.

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)

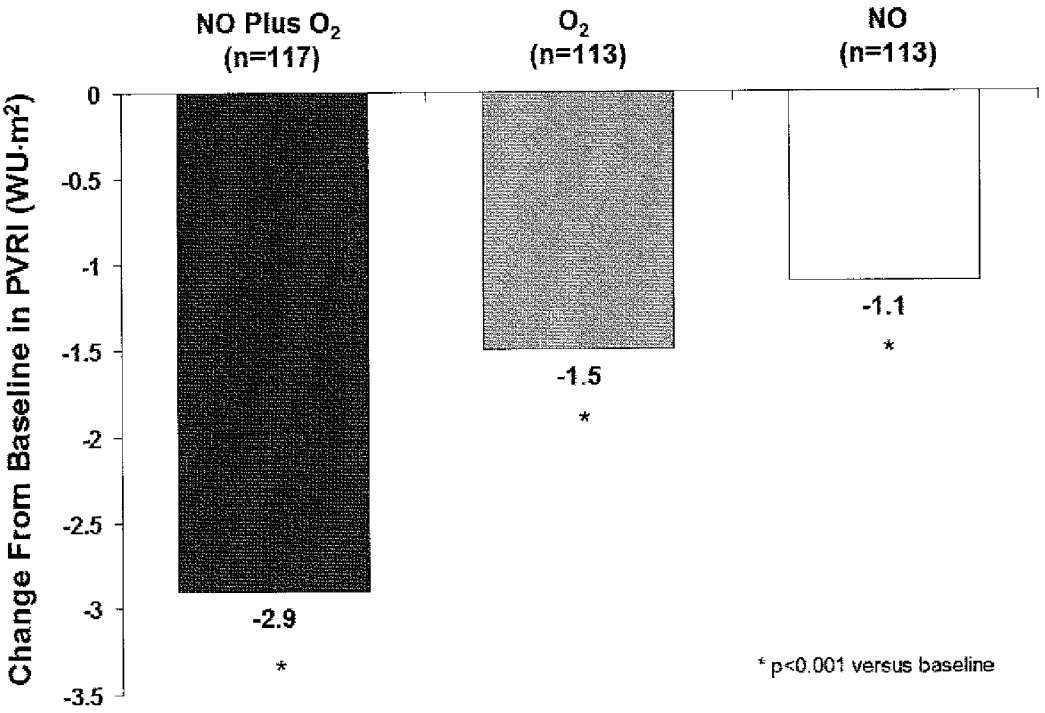


Table 15: PVRI Change From Baseline By Treatment (Intent-to-Treat)

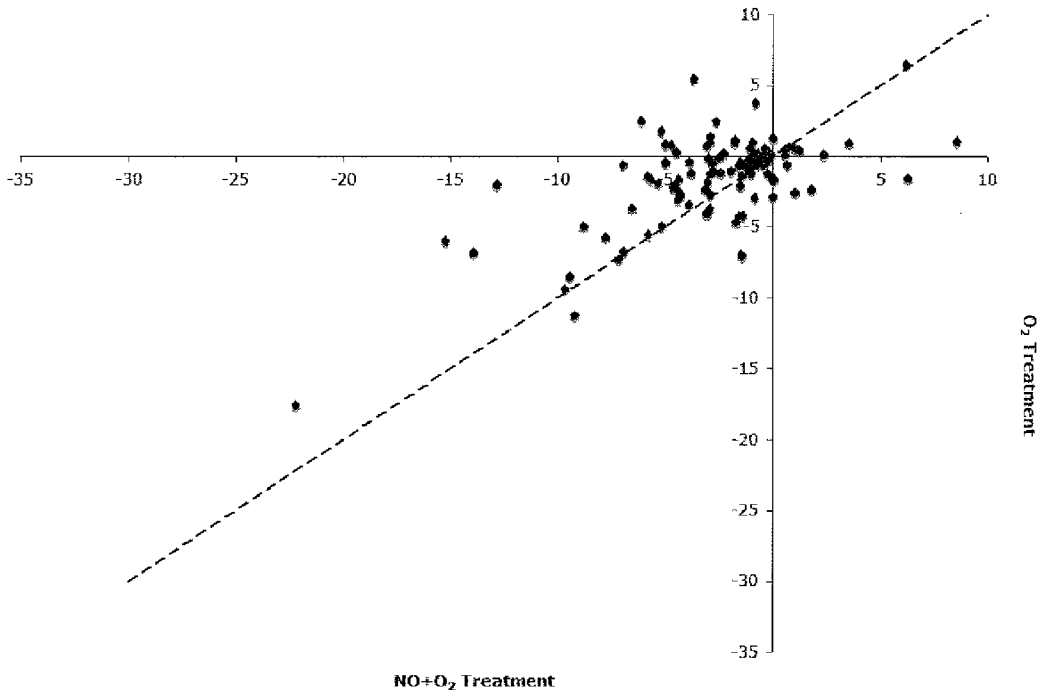
	Treatment		
PVRI ($WU \cdot m^2$)	**NO Plus O_2 (n=117)**	**O_2 (n=113)**	**NO (n=113)**
Baseline (room air)			
Mean	10.8	10.0	10.3
SD	10.30	9.65	10.33
Median	7.5	6.9	6.6
Minimum, maximum	0.5, 54.0	0.5, 47.7	0.9, 54.0
Post-treatment			
Mean	7.8	8.5	9.2
SD	8.75	8.63	10.45
Median	3.6	5.5	5.6
Minimum, maximum	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).

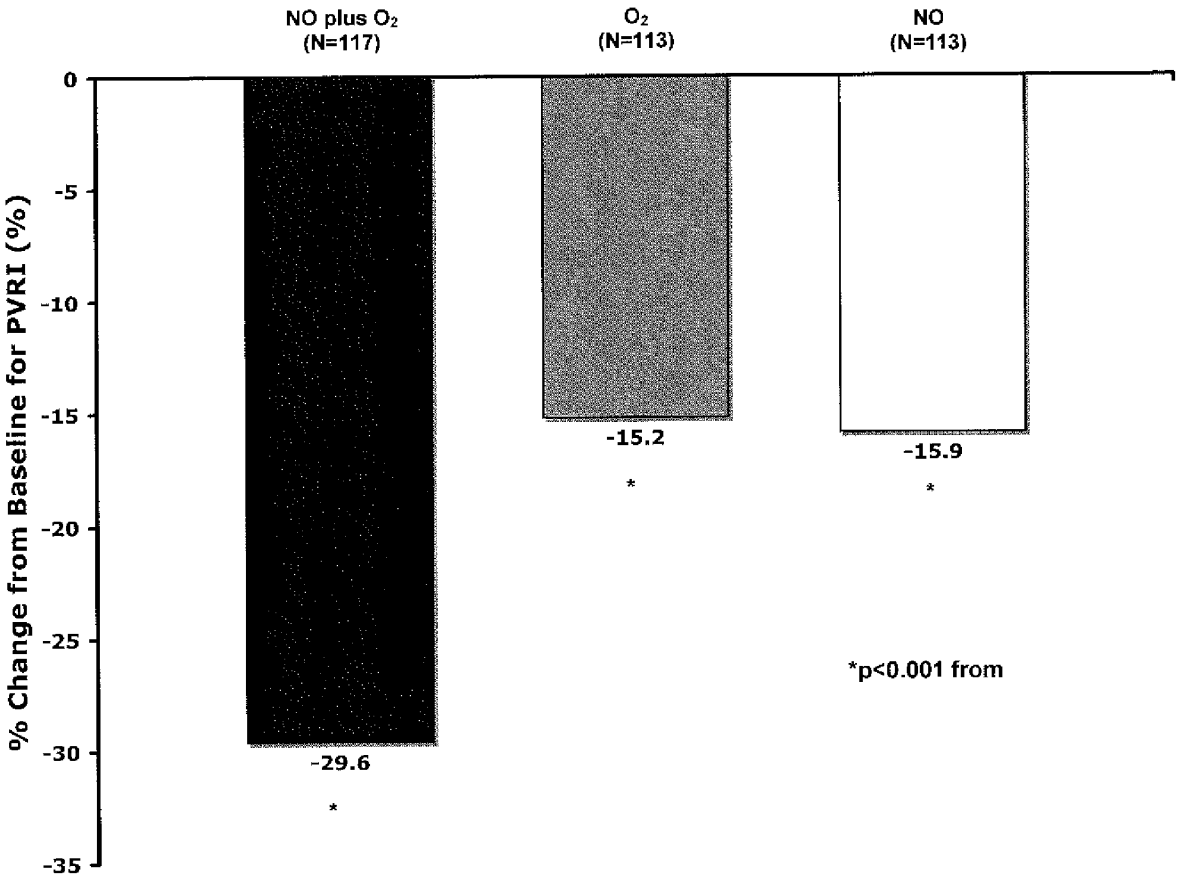
Table 16: PVRI Percent Change From Baseline By Treatment (Intent-to-Treat)

	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·m^2 and actually took study medication. The per-protocol population included all patients who took study medication and had baseline PVRI >3 WU·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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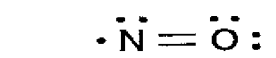
INOmax® (nitric oxide) for inhalation
100 and 800 ppm (parts per million)

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.

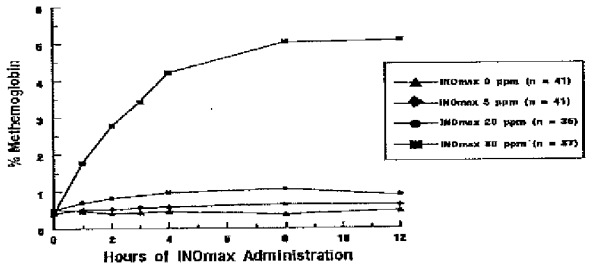
Effects on Pulmonary Vascular Tone in PPHN
Persistent pulmonary hypertension of the newborn (PPHN) occurs as a primary developmental defect or as a condition secondary to other diseases such as meconium aspiration syndrome (MAS), pneumonia, sepsis, hyaline membrane disease, congenital diaphragmatic hernia (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

Electronic Patent Application Fee Transmittal

Application Number:	13683417
Filing Date:	21-Nov-2012
Title of Invention:	METHODS FOR TREATING 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:	26047-0003008

Filed as Large 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	1202	14	80	1120
Independent claims in excess of 3	1201	2	420	840
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Miscellaneous:				
			Total in USD ($)	**1960**

Electronic Acknowledgement Receipt	
EFS ID:	19161724
Application Number:	13683417
International Application Number:	
Confirmation Number:	1654
Title of Invention:	METHODS FOR TREATING 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:	26047-0003008
Receipt Date:	29-MAY-2014
Filing Date:	21-NOV-2012
Time Stamp:	16:31:17
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$1960
RAM confirmation Number	2939
Deposit Account	061050
Authorized User	

File Listing:

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1		Submission.pdf	7684326 823dd740b5db337cb73140e91396a59818e68221	yes	230

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Preliminary Amendment	1	1
	Claims	2	10
	Applicant Arguments/Remarks Made in an Amendment	11	12
	Affidavit-Rule 131-pre-AIA (FTI) ONLY	13	230

Warnings:

Information:

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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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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 13/683,417	Filing Date 11/21/2012	☐ To be Mailed

ENTITY: ☒ LARGE ☐ SMALL ☐ MICRO

APPLICATION AS FILED – PART I

	(Column 1)	(Column 2)		
FOR	NUMBER FILED	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	05/29/2014	(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))	* 44	Minus	** 30	= 14	X $80 =	1120
	Independent (37 CFR 1.16(h))	* 5	Minus	***3	= 2	X $420 =	840
	☐ Application Size Fee (37 CFR 1.16(s))						
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
						TOTAL ADD'L FEE	**1960**

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))						
						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
/ADRIANE WINSTON/

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

NOTICE OF ALLOWANCE AND FEE(S) DUE

94169 7590 06/23/2014

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

EXAMINER
ARNOLD, ERNST V

ART UNIT	PAPER NUMBER
1613	

DATE MAILED: 06/23/2014

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/683,417	11/21/2012	James S. Baldassarre	26047-0003008	1654

TITLE OF INVENTION: METHODS FOR TREATING 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	UNDISCOUNTED	$0	$0	$1770	$0	09/23/2014

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**
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 06/23/2014
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.
13/683,417	11/21/2012	James S. Baldassarre	26047-0003008	1654

TITLE OF INVENTION: METHODS FOR TREATING 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	UNDISCOUNTED	$0	$0	$1770	$0	09/23/2014

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

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/683,417	11/21/2012	James S. Baldassarre	26047-0003008	1654

94169 7590 06/23/2014

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P.O.Box 1022
minneapolis, MN 55440

EXAMINER	
ARNOLD, ERNST V	
ART UNIT	PAPER NUMBER
1613	

DATE MAILED: 06/23/2014

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. 13/683,417	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 *5/29/14*.
   ☐ 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 *1-44*. 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 4/11/13, 4/29/13, 12/12/13 and 5/13/14
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

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 4/11/13 has been entered.

Claims 30-44 are new. Claims 1-44 are pending and under examination.

Information Disclosure Statement

The information disclosure statements (IDSs) submitted on 4/11/13, 4/29/13, 12/12/13 and 5/13/14 were filed after the mailing date of the NOA on 3/1/13. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Withdrawn rejections:

Applicant's Declaration filed under 37 CFR 1.131, amendments and arguments filed 5/29/14 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.

REASONS FOR ALLOWANCE

The following is an examiner's statement of reasons for allowance:

Applicants' IDS submitted on 4/11/13, 4/29/13, 12/12/13 and 5/13/14 did not change the previous determination of patentability.

MPEP 2143.03 states: "All words in a claim must be considered in judging the patentability of that claim against the prior art." *In re Wilson*, 424 F.2d 1382, 1385, 165 USPQ 494, 496 (CCPA 1970). The closest prior art of Rosales et al. (Pediatric Cardiology, 1999, 20:224-226) teaches administration of inhaled nitric oxide at 80 ppm to a 1 month old newborn and Rosales et al. speculated that NO induced pulmonary hypertensive crisis by increasing pulmonary load on a noncompliant left ventricle which could develop pulmonary edema (pages Abstract; Case report 224-225 and 226). However, 80 ppm no is not sufficiently specific to the instantly claimed 20 ppm of NO and there is no guidance or motivation to decrease the treatment dosage of 80 ppm 4 fold to 20 ppm. The Examiner also notes in Preston et al. (Chest 2002; 121:656-659) that an adult patient receiving 20 ppm inhaled NO developed pulmonary edema but had no signs of left heart disease (page 657 and Table 1) and concluded that iNO should be administered at low (≤10 ppm) during careful monitoring (Page 658). Thus, the artisan is directed to administering less than 10 ppm NO for treatment which is less than the

instantly claimed 20 ppm NO. See also the reasons provided in US Patent No's: 8282966 and 8293284.

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

Notice of References Cited	Application/Control No. 13/683,417	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-			
	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	Rosales et al. (Pediatric Cardiology, 1999, 20:224-226)
	V	
	W	
	X	

*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	8	(((baldassarre or rosskamp or ino).in. or INO.as.) and ((inhale or inhaled) with ((nitric adj oxide) or NO)) and (left with (ventricular or ventricle)) and (hypoxic or hypoxia))	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	OFF	2013/01/10 09:22
S2	0	(600/483-485.ccls. and ((inhale or inhaled) with ((nitric adj oxide) or NO)) and (left with (ventricular or ventricle)) and (hypoxic or hypoxia))	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2013/01/10 09:24
S3	19	(424/718.ccls. and ((inhale or inhaled) with ((nitric adj oxide) or NO)) and (left with (ventricular or ventricle)) and (hypoxic or hypoxia))	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2013/01/10 09:25
S4	13	S3 and (neonatal or preterm or infant or baby or babies or premie or premature)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2013/01/10 09:28
S5	1	"5904938".pn. and (neonatal or preterm or infant or baby or babies or premie or premature)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2013/01/10 09:30
S6	6	(128/200.24.ccls. and ((inhale or inhaled) with ((nitric adj oxide) or NO)) and (left with (ventricular or ventricle)) and (hypoxic or hypoxia))	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2013/01/10 14:14
S7	2	"5558083".pn.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2013/02/14 11:37
S8	2	"5651358".pn.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2013/02/14 11:37
S9	2	"6142147".pn.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2013/02/14 11:38
S10	2	"20020185126".pn.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2013/02/14 11:39

S11	2	"20030131848".pn.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2013/02/14 11:39

EAST Search History (Interference)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
S12	0	600/483-485.ccls. and ((inhale or inhaled) with ((nitric adj oxide) or NO)).clm. and ((left with (ventricular or ventricle)) and (hypoxic or hypoxia)).clm.	US-PGPUB; USPAT; UPAD	OR	ON	2013/02/14 11:41
S13	4	424/718.ccls. and ((inhale or inhaled) with ((nitric adj oxide) or NO)).clm. and ((left with (ventricular or ventricle)) and (hypoxic or hypoxia)).clm.	US-PGPUB; USPAT; UPAD	OR	ON	2013/02/14 11:41
S14	2	128/200.24.ccls. and ((inhale or inhaled) with ((nitric adj oxide) or NO)).clm. and ((left with (ventricular or ventricle)) and (hypoxic or hypoxia)).clm.	US-PGPUB; USPAT; UPAD	OR	ON	2013/02/14 11:41

6/16/2014 11:21:04 AM
C:\Users\earnold\Documents\EAST\Workspaces\13683417.wsp

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	13683417
Filing Date	2012-11-21
First Named Inventor	Baldassarre
Art Unit	1613
Examiner Name	Ernst V. Arnold
Attorney Docket Number	26047-0003008

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Receipt date: 05/13/2014	Application Number	13683417 13683417 - GAU: 1613
INFORMATION DISCLOSURE STATEMENT BY APPLICANT	Filing Date	2012-11-21
(Not for submission under 37 CFR 1.99)	First Named Inventor	Baldassarre
	Art Unit	1613
	Examiner Name	Ernst V. Arnold
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/E.A./	1	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)	☐
/E.A./	2	BURKHOFF et al., "Why does pulmonary venous pressure rise after onset of LV dysfunction: a theoretical analysis," Am. J. Physiol., 34:H1819-H1828 (1993)	☐
/E.A./	3	Prior art notice issued in CA267102 on August 9, 2013 (51 pages)	☐
/E.A./	4	FROMM et al., "Congestive Heart Failure and Pulmonary Edema for the Emergency Physician," The Journal of Emergency Medicine, 13(1):71-87 (1995)	☐
/E.A./	5	MOURANI et al., "Left Ventricular Diastolic Dysfunction in Bronchopulmonary Dysplasia," J. of Pediatrics, 152:291-293 (2008)	☐

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Receipt date: 05/13/2014	Application Number	13683417 13683417 - GAU: 1613
INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99**)	Filing Date	2012-11-21
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	Art Unit	1613
	Examiner Name	Ernst V. Arnold
	Attorney Docket Number	26047-0003008

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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)	2014-05-13
Name/Print	Janis K. Fraser	Registration Number	34819

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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.

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CONFIRMATION NO. 1654

SERIAL NUMBER	FILING or 371(c) DATE RULE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
13/683,417	11/21/2012	424	1613	26047-0003008

APPLICANTS
INO THERAPEUTICS LLC, Hampton, NJ

INVENTORS
James S. Baldassarre, Doylestown, PA;

**** CONTINUING DATA ***************************
This application is a CON of 12/820,866 06/22/2010 ABN
which is a CON of 12/494,598 06/30/2009 ABN
This application 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

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

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12/14/2012

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	44 ~~30~~	5 ~~3~~

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

TITLE
METHODS FOR TREATING PATIENTS WHO ARE CANDIDATES FOR INHALED NITRIC OXIDE TREATMENT

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Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13683417	BALDASSARRE ET AL.
	Examiner	Art Unit
	ERNST 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	1/10/13	eva
600	483-485text limited	1/10/13	eva

SEARCH NOTES		
Search Notes	Date	Examiner
inventor/assignee name EAST/PALM	1/10/13	eva
EAST all databases	1/10/13	eva
search update EAST all databases	2/14/13	eva
updated IDS	2/14/13	eva
updated IDS	6/16/14	eva

INTERFERENCE SEARCH			
US Class/ CPC Symbol	US Subclass / CPC Group	Date	Examiner
128	200.24 text limited	2/14/13	eva
424	718 text limited	2/14/13	eva
600	483-485 text limited	2/14/13	eva

718	

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99)**		
	Application Number	13683417
	Filing Date	2012-11-21
	First Named Inventor	Baldassarre
	Art Unit	1613
	Examiner Name	
	Attorney Docket Number	26047-0003008

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	First Named Inventor	Baldassarre
	Art Unit	1613
	Examiner Name	
	Attorney Docket Number	26047-0003008

/E.A./	1	Canadian Intellectual Property Office, Requisition by the examiner in CA Appl. 2,671,029; Apr. 25, 2013; 24 pp.	☐
/E.A./	2	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	☐
/E.A./	3	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)	☐
/E.A./	4	Description of the clinical trial NCT00626028 published online on the website http://clinicaltrials.gov/archive/ NCT00626028; Feb. 28, 2008.	☐
/E.A./	5	Bernasconi et al.; Inhaled Nitric Oxide Applications in Peadiatric Practice, Images in Pediatric Cardiology, Vol. 4(1), Jan-Mar 2002; pages 4-29.	☐
/E.A./	6	Torys LLP, Letter to Canadian Commissioner of Patents relating to CA 2,671,029; Aug. 9, 2013;	☐
/E.A./	7	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)	☐
/E.A./	8	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)	☐
/E.A./	9	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)	☐
/E.A./	10	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	☐
/E.A./	11	Weinberger et al., Pulmonary Hypertension, Chapter 14 of Principles of Pulmonary Medicine, Elsevier Saunders, 2014; pp 189-200	☐

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

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	Examiner Name	
	Attorney Docket Number	26047-0003008

/E.A./	12	Hayward et al., Inhaled nitric oxide in cardiology practice; Cardiovascular Research 43:628-638 (1999)	☐
	13		☐

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Signature	/Janis K. Fraser/	Date (YYYY-MM-DD)	2013-12-12
Name/Print	Janis K. Fraser	Registration Number	34819

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	Examiner	Art Unit
	ERNST 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	02/14/2013	06/16/2014							
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Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13683417	BALDASSARRE ET AL.
	Examiner	**Art Unit**
	ERNST 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	02/14/2013	06/16/2014							
	37		=							
	38		=							
	39		=							
	40		=							
	41		=							
	42		=							
	43		=							
	44		=							

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13683417	BALDASSARRE ET AL.
	Examiner	**Art Unit**
	ERNST ARNOLD	1613

CPC							
Symbol						**Type**	**Version**
A61M		16	/	12		I	2013-01-01
A61B		8	/	48		I	2013-01-01
A61K		45	/	06		I	2013-01-01
G06Q		99	/	00		I	2013-01-01
A61K		33	/	00		F	2013-01-01
A61K		31	/	21		I	2013-01-01
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CPC Combination Sets								
Symbol					**Type**	**Set**	**Ranking**	**Version**
A61K		33	/	00	I	2	1	2013-01-01
A61K		2300	/	00	A	2	2	2013-01-01
A61K		2300	/	00	A	1	2	2013-01-01
A61K		31	/	21	I	1	1	2013-01-01

NONE		**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	44	
/ERNST ARNOLD/ Primary Examiner.Art Unit 1613	6/16/14	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	none

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13683417	BALDASSARRE ET AL.
	Examiner	**Art Unit**
	ERNST ARNOLD	1613

US ORIGINAL CLASSIFICATION	
CLASS	SUBCLASS
424	718

CROSS REFERENCE(S)					
CLASS	SUBCLASS (ONE SUBCLASS PER BLOCK)				
128	200.24				
423	405				
600	483	484	485		

INTERNATIONAL CLASSIFICATION										
CLAIMED					NON-CLAIMED				
A	6	1	B	5 / 02 (2006.01.01)	A	6	1	M	16 / 00 (2006.01.01)
A	0	1	N	59 / 00 (2006.01.01)					
A	6	1	K	33 / 00 (2006.01.01)					
C	0	1	B	21 / 24 (2006.01.01)					

NONE		Total Claims Allowed: 44	
(Assistant Examiner)	(Date)		
/ERNST ARNOLD/ Primary Examiner.Art Unit 1613	6/16/14	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	none

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13683417	BALDASSARRE ET AL.
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Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original

NONE (Assistant Examiner)	(Date)	**Total Claims Allowed:** 44	
/ERNST ARNOLD/ Primary Examiner.Art Unit 1613 (Primary Examiner)	6/16/14 (Date)	O.G. Print Claim(s) 1	O.G. Print Figure none

U.S. Patent and Trademark Office Part of Paper No. 20140616

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	13683417
Filing Date	2012-11-21
First Named Inventor	Baldassarre
Art Unit	1613
Examiner Name	Ernst V. Arnold
Attorney Docket Number	26047-0003008

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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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							☐

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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]

EFS Web 2.1.17

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

Receipt date: 04/11/2013	Application Number	13683417 13683417 - GAU: 1613
INFORMATION DISCLOSURE STATEMENT BY APPLICANT	Filing Date	2012-11-21
(Not for submission under 37 CFR 1.99)	First Named Inventor	Baldassarre
	Art Unit	1613
	Examiner Name	Ernst V. Arnold
	Attorney Docket Number	26047-0003008

/E.A./	1	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)	☒
/E.A./	2	Communication from Canadian Intellectual Property Office dated March 19, 2013, enclosing Protest from Robic regarding Canadian patent application no. 2,671,029 (42 pages)	☐
/E.A./	3	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)	☐
/E.A./	4	Hess, "Heliox and Inhaled Nitric Oxide," Mechanical Ventilation, Chapter 28 (2001), pages 454-480	☐

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	06/16/2014

*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: 04/11/2013	Application Number	13683417	13683417 - GAU: 1613
INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99**)	Filing Date	2012-11-21	
	First Named Inventor	Baldassarre	
	Art Unit	1613	
	Examiner Name	Ernst V. Arnold	
	Attorney Docket Number	26047-0003008	

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)	2013-03-26
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./

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	13683417
Filing Date	2012-11-21
First Named Inventor	Baldassarre
Art Unit	1613
Examiner Name	Ernst V. Arnold
Attorney Docket Number	26047-0003008

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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
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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]
	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]

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Receipt date: 04/29/2013	Application Number	13683417 13683417 - GAU: 1613
INFORMATION DISCLOSURE STATEMENT BY APPLICANT	Filing Date	2012-11-21
(Not for submission under 37 CFR 1.99)	First Named Inventor	Baldassarre
	Art Unit	1613
	Examiner Name	Ernst V. Arnold
	Attorney Docket Number	26047-0003008

/E.A./	1	Free Merriam-Webster Dictionary, definition of "supplying", pages 1-4, downloaded April 22, 2013	☐
/E.A./	2	Himashree et al., "Nitric oxide and the respiratory system," Current Science, Vol. 85, No. 5, September 10, 2003, pages 607-614	☐
/E.A./	3	Kazerooni, Cardiopulmonary Imaging 2004, Lippincott Williams & Wilkins, "Left Ventricular Function", pages 234 and 236 (in part)	☐
/E.A./	4	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	☐
/E.A./	5	Loh et al., "Cardiovascular Effects of Inhaled Nitric Oxide in Patients With Left Ventricular Dysfunction," Circulation, Vol. 90, pages 2780-2785 (1994)	☐
/E.A./	6	McLaughlin et al., "Pulmonary Arterial Hypertension," Circulation, Vol. 114, pages 1417-1431 (2006)	☐

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	06/16/2014

*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.

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	Art Unit	1613	
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☐ A certification statement is not submitted herewith.

SIGNATURE

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Signature	/Janis K. Fraser/	Date (YYYY-MM-DD)	2013-04-29
Name/Print	Janis K. Fraser	Registration Number	34819

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

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 06/23/2014

FISH & RICHARDSON P.C.
P.O. BOX 1022
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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.
13/683,417	11/21/2012	James S. Baldassarre	26047-0003008	1654

TITLE OF INVENTION: METHODS FOR TREATING 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	LARGE	$0	$0	$1770	$0	09/23/2014

EXAMINER	ART UNIT	CLASS-SUBCLASS
ARNOLD, ERNST V.	1613	424-71800

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 _____

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[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 June 27, 2014

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

23246677.doc

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Named Inventor	:	James S. Baldassarre	Art Unit	:	1613
Serial No.	:	13/683,417	Examiner	:	Ernst V. Arnold
Filed	:	November 21, 2012	Confirmation No.	:	1654
			Notice of Allowance Date: June 23, 2014		
Title	:	METHODS FOR TREATING PATIENTS WHO ARE CANDIDATES FOR INHALED NITRIC OXIDE TREATMENT			

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

RESPONSE TO NOTICE OF ALLOWANCE

In response to the Notice of Allowance mailed June 23, 2014, enclosed is a completed Part B - Fee(s) Transmittal.

The issue fee was previously paid on March 8, 2013, so no further fees are believed due. Apply any necessary charges or credits to Deposit Account 06-1050, referencing the above attorney docket number.

COMMENTS ON EXAMINER'S REASONS FOR ALLOWANCE

It is recognized that in accordance with M.P.E.P. § 1302.14, the Examiner's reasons for allowance need not set forth all of the details as to why the claims are allowed. In the above-referenced application, it is not conceded that the Examiner's stated reasons for allowance are the only reasons for which the claims are allowable. The Examiner's reasons for allowance indicate that particular claim elements are not disclosed or suggested by certain prior art of record. The claims may be patentable for other reasons as well, including the inventive combination of all of the recited claim elements. It is not conceded that the specific limitations identified by the Examiner are necessary to distinguish the art of record or to satisfy the requirements of 35 U.S.C. § 112. Moreover, the Examiner does not assert, and it would not be conceded, that the Examiner's reasons have any bearing on the patentability of claims in any other applications directed to the disclosed subject matter.

In addition, each dependent claim stands on its own and may be allowable on its own merits. In particular, each dependent claim may be allowable on the basis of a combination of

some of the features recited in the dependent claim and its base claim(s), which combination of features may not include all of the limitations identified in the Examiner's reasons for allowance.

Respectfully submitted,

Date: June 27, 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

23246673.doc

Electronic Acknowledgement Receipt	
EFS ID:	19439079
Application Number:	13683417
International Application Number:	
Confirmation Number:	1654
Title of Invention:	METHODS FOR TREATING 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:	26047-0003008
Receipt Date:	27-JUN-2014
Filing Date:	21-NOV-2012
Time Stamp:	15:51:37
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	Issue Fee Payment (PTO-85B)	85.pdf	108414 5fed020639123cf458333083e42b48f7e0e94b65	no	1
Warnings:					
Information:					

2	Post Allowance Communication - Incoming	Response.pdf	65640 0d78fc45eb541cece7b8d4fa43d8d6e33dc44a6f	no	2

Warnings:	
Information:	
Total Files Size (in bytes):	174054

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.

Best Available Copy

1 fm

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 06/23/2014

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.
13/683,417	11/21/2012	James S. Baldassarre	26047-0003008	1654

TITLE OF INVENTION: METHODS FOR TREATING 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	LARGE	$0	$0	$1770	$0	09/23/2014

EXAMINER	ART UNIT	CLASS-SUBCLASS
ARNOLD, ERNST V.	1613	424-71800

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 June 27, 2014

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

23246677.doc

06/30/2014 EEKUBAY2 00000010 061050 13683417

01 FC:1501 960.00 DA
02 FC:1508 810.00 DA

Adjustment date: 06/30/2014 EEKUBAY2
03/11/2013 INTEFSW 00000414 061050 13683417
01 FC:1501 1770.00 CR

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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APPLICATION NO.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/683,417	08/05/2014	8795741	26047-0003008	1654

94169 7590 07/16/2014

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):

James S. Baldassarre, Doylestown, PA;
INO THERAPEUTICS LLC, Hampton, NJ

AO 120 (Rev. 08/10)

TO:	REPORT ON THE FILING OR DETERMINATION OF AN ACTION REGARDING A PATENT OR TRADEMARK
Mail Stop 8 Director of the U.S. Patent and Trademark Office P.O. Box 1450 Alexandria, VA 22313-1450	

In Compliance with 35 U.S.C. § 290 and/or 15 U.S.C. § 1116 you are hereby advised that a court action has been filed in the U.S. District Court for the District of Delaware on the following

☐ Trademarks or ☑ Patents. (☐ the patent action involves 35 U.S.C. § 292.):

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
	2/19/2015	for the District of Delaware

PLAINTIFF	DEFENDANT
INO THERAPEUTICS LLC and IKARIA, INC.	PRAXAIR DISTRIBUTION, INC. and PRAXAIR, INC.

	PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1	8,282,966 B2	10/9/2012	INO Therapeutics LLC
2	8,293,284 B2	10/23/2012	INO Therapeutics LLC
3	8,431,163 B2	4/30/2013	INO Therapeutics LLC
4	8,795,741 B2	8/5/2014	INO Therapeutics LLC
5	8,846,112 B2	9/30/2014	INO Therapeutics LLC

In the above—entitled case, the following patent(s)/ trademark(s) have been included:

DATE INCLUDED	INCLUDED BY ☐ Amendment ☐ Answer ☐ Cross Bill ☐ Other Pleading	
PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1		
2		
3		
4		
5		

In the above—entitled case, the following decision has been rendered or judgement issued:

DECISION/JUDGEMENT

CLERK	(BY) DEPUTY CLERK	DATE

Copy 1—Upon initiation of action, mail this copy to Director **Copy 3—Upon termination of action, mail this copy to Director**
Copy 2—Upon filing document adding patent(s), mail this copy to Director **Copy 4—Case file copy**

ADDENDUM TO AO 120 (ADDITIONAL PATENTS)

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
	2/19/2015	for the District of Delaware

PLAINTIFF	DEFENDANT
INO THERAPEUTICS LLC and IKARIA, INC.	PRAXAIR DISTRIBUTION, INC. and PRAXAIR, INC.

	PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
6	8,291,904 B2	10/23/2012	INO Therapeutics LLC
7	8,573,210 B2	11/5/2013	INO Therapeutics LLC
8	8,573,209 B2	11/5/2013	INO Therapeutics LLC
9	8,776,794 B2	7/15/2014	INO Therapeutics LLC
10	8,776,795 B2	7/15/2014	INO Therapeutics LLC

Trials@uspto.gov
571.272.7822

Paper 12 (IPR2015-00522)
Paper 12 (IPR2015-00524)
Paper 12 (IPR2015-00525)
Paper 12 (IPR2015-00526)
Entered: July 29, 2015

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

PRAXAIR DISTRIBUTION, INC.,
Petitioner,

v.

INO THERAPEUTICS, INC.,
Patent Owner.

Case IPR2015-00522 (8,282,966 B2)
Case IPR2015-00524 (8,293,284 B2)
Case IPR2015-00525 (8,431,163 B2)
Case IPR2015-00526 (8,795,741 B2)[1]

Before LORA M. GREEN, TINA E. HULSE, and ROBERT A. POLLOCK, *Administrative Patent Judges.*

HULSE, *Administrative Patent Judge.*

DECISION
Denying Institution of *Inter Partes* Review
37 C.F.R. § 42.108

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[1] This Decision addresses issues that are common to each of the above-referenced cases. We, therefore, issue a single Decision that has been entered in each case. The parties may use this style caption when filing a single paper in multiple proceedings, provided that such caption includes a footnote attesting that "the word-for-word identical paper is filed in each proceeding identified in the caption."

I. INTRODUCTION

Petitioner, Praxair Distribution, Inc., filed Petitions requesting an *inter partes* review of: (1) claims 1–29 of U.S. Patent No. 8,282,966 ("the '966 patent") (Ex. 1001, IPR2015-00522); (2) claims 1–30 of U.S. Patent No. 8,293,284 B2 ("the '284 patent") (Ex. 1001, IPR2015-00524); (3) claims 1–25 of U.S. Patent No. 8,431,163 B2 ("the '163 patent") (Ex. 1001, IPR2015-00525); and (4) claims 1–44 of U.S. Patent No. 8,795,741 B2 ("the '741 patent") (Ex. 1001, IPR2015-00526). Paper 1 (IPR2015-00522) ("-522 Pet.").[2] Patent Owner, INO Therapeutics LLC, filed a Preliminary Response to each Petition. Paper 8 (IPR2015-00522) ("-522 Prelim. Resp.").[3]

We have jurisdiction under 35 U.S.C. § 314, which provides that an *inter partes* review may not be instituted "unless . . . there is a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition." 35 U.S.C. § 314(a). Upon considering the Petitions and Preliminary Responses, we determine that Petitioner has not established a reasonable likelihood that it would prevail in showing the unpatentability of any of the challenged claims in any of the proceedings. Accordingly, the Petition in each proceeding is *denied*.

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[2] Petitioner filed Petitions as Paper 1 in each of the other proceedings. We refer to those Petitions as "-524 Pet.," "-525 Pet.," and "-526 Pet."

[3] Patent Owner filed Preliminary Responses as Paper 8 in each of the other proceedings. We refer to those Preliminary Responses as "-524 Prelim. Resp.," "-525 Prelim. Resp.," and "-526 Prelim. Resp."

A. Related Proceedings

Petitioner states that it is not aware of any current litigation involving any of the involved patents. -522 Pet. 7.[4]

B. The Involved Patents

The involved patents are all related and share substantially the same Specification. The Specification discloses methods of reducing the risk of an adverse event, such as pulmonary edema, associated with treating a patient with inhaled nitric oxide gas ("iNO"). Ex. 1001, Abstract. Nitric oxide is a lung-specific vasodilator that significantly improves blood oxygenation and reduces the need for extracorporeal oxygenation. *Id.* at 3:33–42. INOmax®—nitric oxide for inhalation—is an FDA-approved drug for treatment of term and near term (>34 weeks gestation) neonates who have hypoxic respiratory failure associated with evidence of pulmonary hypertension, known as persistent pulmonary hypertension in the newborn ("PPHN"). *Id.* at 1:18–22, 6:23–29.

The Specification also describes the INOT22 Study, which was conducted, in part, to assess the safety and effectiveness of INOmax® in patients four weeks to eighteen years of age undergoing assessment of pulmonary hypertension. *Id.* at 9:18–30, 43–44. Initially, the study protocol did not include a baseline pulmonary capillary wedge pressure ("PCWP") value as an exclusion criteria.[5] *Id.* at 12:25–26. During the study, at least

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[4] Petitioner makes similar arguments in its papers and cites similar evidence in each of the cases. Accordingly, citations to papers and exhibits in this Decision refer to those filed in IPR2015-00522, unless stated otherwise.

[5] PCWP provides an estimate of left atrial pressure, which may be used to diagnose the severity of left ventricular dysfunction and to measure pulmonary hypertension. Ex. 1001, 5:9–18.

two patients developed signs of pulmonary edema. *Id.* at 13:2–3. The Specification states that "[t]his is of interest because pulmonary edema has previously been reported with the use of iNO in patients with LVD [left ventricular dysfunction], and may be related to decreasing PVR [pulmonary vascular resistance] and overfilling of the left atrium." *Id.* at 13:3–6. The Specification further states that "after the surprising and unexpected identification of SAEs [serious adverse events] in the early tested patients, it was determined that patients with pre-existing LVD had an increased risk of experiencing an AE or SAE [such as pulmonary edema] upon administration." *Id.* at 12:26–30, 13:62–64. The study protocol was amended to exclude patients with a baseline PCWP greater than 20 mmHg, which was selected to avoid enrolling children with LVD who "would be most likely at-risk for these SAEs." *See id.* at 12:32–38.

C. Illustrative Claim

Petitioner challenges: (1) claims 1–29 the '966 patent (IPR2015-00522); (2) claims 1–30 of the '284 patent (IPR2015-00524); (3) claims 1–25 of the '163 patent (IPR2015-00525); and (4) claims 1–44 of the '741 patent (IPR2015-00526). The challenged claims are all similar. Claim 1 of the '966 patent is illustrative and is reproduced below:

> 1. A method of reducing the risk of occurrence of pulmonary edema associated with a medical treatment comprising inhalation of 20 ppm nitric oxide gas, said method comprising:
>
> (a) performing echocardiography to identify a child in need of 20 ppm inhaled nitric oxide treatment for pulmonary hypertension, wherein the child is not dependent on right-to-left shunting of blood;
>
> (b) determining that the child identified in (a) has a pulmonary capillary wedge pressure greater than or equal to 20 mm Hg and thus has left ventricular dysfunction, so

> is at particular risk of pulmonary edema upon treatment with inhaled nitric oxide; and
>
> (c) excluding the child from inhaled nitric oxide treatment, based on the determination that the patient has left ventricular dysfunction and so is at particular risk of pulmonary edema upon treatment with inhaled nitric oxide.

Common among almost all the independent claims of all the involved patents is a limitation like step (c) of claim 1 above, which excludes a patient from treatment with inhaled nitric oxide based on a determination that the patient has left ventricular dysfunction and so is at particular risk of pulmonary edema upon treatment with inhaled nitric oxide. *See* claims 1(c),[6] 6(c), 13(e), and 22(e) of the '966 patent (Ex. 1001, IPR2015-00522); claims 1(c), 6(c), 13(e), and 23(e) of the '284 patent (Ex. 1001, IPR2015-00524); claims 1(c) and 6(e) of the '163 patent (Ex. 1001, IPR2015-00525); claims 1(e) and 34(e) of the '741 patent (Ex. 1001, IPR2015-00526).

However, not all of the independent claims recite the exact language as claim 1(c) above. Certain claims recite excluding a patient from treatment with inhaled nitric oxide or, despite the patient's ongoing need for treatment for hypoxic respiratory failure, discontinuing treatment with inhaled nitric oxide after it has begun, where the exclusion or discontinuation is based on a determination that the patient has left ventricular dysfunction and so is at particular risk of pulmonary edema upon treatment with inhaled nitric oxide. *See* claims 12(c) and 20(e) of the '163 patent (Ex. 1001, IPR2015-00525); claims 9(e) and 37(e) of the '741 patent

---

[6] For ease of reference, we refer to particular steps of particular claims, e.g., step (c) of claim 1, as "claim 1(c)."

(Ex. 1001, IPR2015-00526). Additionally, claim 24 of the '741 patent recites "(d) determining that a second patient . . . has pre-existing left ventricular dysfunction, so is at particular risk of increased PCWP leading to pulmonary edema upon treatment with inhaled nitric oxide" and then "(e) administering a second treatment regimen to the second patient [determined to have LVD], 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." Ex. 1001, claim 24 (IPR2015-00526).

Despite the differences in claim language, we interpret the above "exclusion limitations" to all require excluding a patient from inhaled nitric oxide treatment—either by never treating the patient or discontinuing treatment—after determining that the patient has left ventricular dysfunction and so is at particular risk of pulmonary edema upon treatment with inhaled nitric oxide.

D. The Asserted Grounds of Unpatentability

In IPR2015-00522, Petitioner challenges the patentability of claims 1–29 of the '966 patent on the following grounds (-522 Pet. 14–58):

References	Basis	Claims Challenged
Bernasconi,[7] INOmax label,[8] Loh,[9] and Goyal[10]	§ 103	1–3, 5–9, 11, 13–17, 20, 22–25, and 28

[7] A. Bernasconi and M. Beghetti, *Inhaled Nitric Oxide Applications in Paediatric Practice*, 4 IMAGES PAEDIATR. CARDIOL. 4–29 (2002) (Ex. 1004).

[8] Final Printed Labeling for INOmax™ (nitric oxide) for inhalation (Ex. 1014).

References	Basis	Claims Challenged
Bernasconi, INOmax label, Loh, Goyal, and Macrae[11]	§ 103	4, 10, 12, 18, 19, 21, 26, 27, and 29
Ichinose,[12] Neonatal Group,[13] Macrae, Loh, Goyal, and Germann[14]	§ 103	1–29

In IPR2015-00524, Petitioner challenges the patentability of claims 1–30 of the '284 patent on the following grounds (-524 Pet. 12–56):

References	Basis	Claims Challenged
Bernasconi, INOmax label, Loh, and Goyal	§ 103	1–3, 5–9, 11, 13, 14, 16–18, 21, 23–27, and 29
Bernasconi, INOmax label, Loh, Goyal, and Macrae	§ 103	4, 10, 12, 15, 19, 20, 22, 28, and 30

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[9] E. Loh et al., *Cardiovascular Effects of Inhaled Nitric Oxide in Patients with Left Ventricular Dysfunction*, 90 CIRCULATION 2780–85 (1994) (Ex. 1006).

[10] P. Goyal et al., *Efficacy of Nitroglycerin Inhalation in Reducing Pulmonary Arterial Hypertension in Children with Congenital Heart Disease*, 97 BRITISH J. ANESTHESIA 208–14 (2006) (Ex. 1007).

[11] D. J. Macrae et al., *Inhaled Nitric Oxide Therapy in Neonates and Children: Reaching a European Consensus*, 30 INTENSIVE CARE MED. 372–80 (2004) (Ex. 1008).

[12] F. Ichinose et al., *Inhaled Nitric Oxide: A Selective Pulmonary Vasodilator: Current Uses and Therapeutic Potential*, 109 CIRCULATION 3106–11 (2004) (EX. 1009).

[13] The Neonatal Inhaled Nitric Oxide Study Group, *Inhaled Nitric Oxide in Full-Term and Nearly Full-Term Infants with Hypoxic Respiratory Failure*, 336 NEW ENG. J. MED. 597–604 (1997) (Ex. 1011).

[14] P. Germann et al., *Inhaled Nitric Oxide Therapy in Adults: European Expert Recommendations*, 31 INTENSIVE CARE MED. 1029–41 (2005) (EX. 1010).

References	Basis	Claims Challenged
Ichinose, Neonatal Group, Macrae, Loh, Goyal, and Germann	§ 103	1–30

In IPR2015-00525, Petitioner challenges the patentability of claims 1–25 of the '163 patent on the following grounds (-525 Pet. 12–54):

References	Basis	Claims Challenged
Bernasconi, INOmax label, Loh, and Goyal	§ 103	1, 2, 4, 6, 7, 9, 11–13, 15, 18, 20, 21, 23, and 25
Bernasconi, INOmax label, Loh, Goyal, and Macrae	§ 103	3, 5, 8, 10, 14, 16, 17, 19, 22, and 24
Ichinose, Macrae, Germann, Neonatal Group, Loh, and Goyal	§ 103	1–25

In IPR2015-00526, Petitioner challenges the patentability of claims 1–44 of the '741 patent on the following grounds (-526 Pet. 13–60):

References	Basis	Claims Challenged
Bernasconi, Loh, and Goyal	§ 103	1, 2, 4, 6–14, 17–23, 31, 32, 34–35, 37–40, and 42–44
Bernasconi, Loh, INOmax label, Juliana,[15] and Goyal	§ 103	24–27, 29, 30, and 33
Bernasconi, Loh, Macrae, and Goyal	§ 103	3, 5, 15, 16, 36, and 41
Bernasconi, Loh, INOmax label, Juliana, Macrae, and Goyal	§ 103	28

[15] A. Juliana and F. Abbad, *Severe Persistent Pulmonary Hypertension of the Newborn in a Setting Where Limited Resources Exclude the Use of Inhaled Nitric Oxide: Successful Treatment with Sildenafil*, 164 EUR. J. PEDIATR. 626–29 (2005) (Ex. 1032, IPR2015-00526).

References	Basis	Claims Challenged
Ichinose, Neonatal Group, Macrae, Loh, Germann, and Goyal	§ 103	1–23, 31, 32, and 34–44
Ichinose, Neonatal Group, Macrae, Loh, INOmax label, Germann, and Goyal	§ 103	24–30 and 33

II. ANALYSIS

A. Claim Construction

In an *inter partes* review, the Board interprets claim terms in an unexpired patent according to the broadest reasonable construction in light of the specification of the patent in which they appear. *See In re Cuozzo Speed Techs., LLC*, No. 2014-1301, 2015 WL 4097949, at *5–*8 (Fed. Cir. July 8, 2015); 37 C.F.R. § 42.100(b). Under that standard, and absent any special definitions, we give claim terms their ordinary and customary meaning, as would be understood by one of ordinary skill in the art at the time of the invention. *See In re Translogic Tech., Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007). Any special definitions for claim terms must be set forth with reasonable clarity, deliberateness, and precision. *See In re Paulsen*, 30 F.3d 1475, 1480 (Fed. Cir. 1994).

1. "child" and "children"

The term "child" or "children" appears in each of the independent claims of the '966 patent and independent claims 34 and 37 of the '741 patent. Ex. 1001, claims 1, 6, 13, and 22 (IPR2015-00522); Ex. 1001, claims 34 and 37 (IPR2015-00526).

Petitioner asserts that the Specification states that "the term 'children' (and variations thereof) ***includes*** those being around 4 weeks to 18 years of age." -522 Pet. 10 (quoting Ex. 1001, 4:13–14). Given the word "includes,"

Petitioner argues that the term "children" is not limited to children in that age range. Additionally, Petitioner notes that dependent claims 2 and 8 specify that "the child is a neonate," therefore confirming that the age range for a "child" is broader than the range stated in the Specification. *Id.*

Patent Owner argues that the term "child" does not include human beings prior to birth. -522 Prelim. Resp. 21. Patent Owner also notes that the Specification defines adults as "those over 18 years of age." *Id.* (quoting Ex. 1001, 4:15–16). Because the Specification defines patients who are over 18 years of age as adults, Patent Owner contends that the terms "child" and "children" should be construed to mean "humans from birth until 18 years of age." *Id.* at 23.

We find Patent Owner's arguments persuasive and determine that Patent Owner's proposed construction is the broadest reasonable interpretation in light of the Specification.

2. "term or near-term neonate"

The claim phrase "term or near-term neonate" appears in each of the independent claims of the '284 patent and the '163 patent. Ex. 1001, claims 1, 6, 13, and 23 (IPR2015-00524); Ex. 1001, claims 1, 6, 12, and 20 (IPR2015-00525). The phrase also appears in independent claims 1, 9, and 24 of the '741 patent. Ex. 1001, claims 1, 9, and 24 (IPR2015-00526).

Petitioner does not offer a specific construction for this term. Patent Owner, however, relies on the Specification and medical dictionary definitions to assert the following constructions for the following terms: (1) "neonate" is "an infant aged 1 month or younger"; (2) "near-term" is "greater than around 34 weeks gestation"; and (3) "term" is "between around 37 and around 40 weeks gestation." -524 Prelim. Resp. 21–22. Specifically, Patent Owner notes that the Specification states that "near term neonates"

are those having achieved "> 34 weeks gestation." *Id.* at 21 (citing -524 Ex. 1001, 6:27–28). Patent Owner also provides medical dictionary definitions for the term "infant" and "neonate" that are consistent with its proposed constructions. *Id.* (citing Ex. 2007, 967–68, 1288).

We find Patent Owner's arguments persuasive and determine that Patent Owner's proposed constructions are the broadest reasonable interpretation in light of the Specification. That is, we construe the phrase "term or near-term neonate" to mean "an infant aged 1 month or younger born between around 37 and 40 weeks gestation or greater than around 34 weeks gestation."

B. Obviousness of the '966 Patent, the '284 Patent, the '163 Patent, and certain of the '741 Patent Claims over Bernasconi, INOmax Label, Loh, and Goyal

Petitioner asserts that each of the independent claims in the '966 patent, the '284 patent, and the '163 patent is unpatentable as obvious over Bernasconi, INOmax label, Loh, and Goyal. -522 Pet. 14–32. Petitioner also asserts that independent claims 1, 9, 34, and 37 of the '741 patent are unpatentable as obvious over Bernasconi, Loh, and Goyal. -526 Pet. 13–25. As support, Petitioner submits the testimony of Dr. Maurice Beghetti in each proceeding. Ex. 1002. Patent Owner opposes Petitioner's assertions. *See, e.g.*, -522 Prelim. Resp. 35–50. We determine, on the current record, that Petitioner has not established a reasonable likelihood that it would prevail in showing any of those challenged claims is unpatentable as obvious over the cited prior art.

1. Bernasconi (Ex. 1004)

Bernasconi reviews the "delivery and monitoring aspects of inhaled nitric oxide, its potential toxic and side effects and its applications in several

cardiopulmonary disorders in paediatrics." Ex. 1004, Abstract; *see also* Title. Bernasconi states that "[d]ose response studies have been performed in persistent pulmonary hypertension of the newborn (PPHN)" and that "[t]he recommended dose by the FDA for the treatment of neonatal hypoxic respiratory failure is 20 ppm." *Id.* at 3. Bernasconi also states that

> PPHN is a syndrome associated with diverse neonatal cardiopulmonary disorders, which are characterised by a high pulmonary vascular resistance with right to left shunt of deoxygenated blood across the ductus arteriosus and/or the foramen ovale. The role of echocardiography to confirm the diagnosis and conduct therapy is therefore essential. Echocardiography also excludes structural congenital heart disease, which would contraindicate the use of iNO.

Id. at 8.

Bernasconi also teaches that iNO may lead to pulmonary edema in patients with LVD and, thus, emphasizes a need for "careful observation and intensive monitoring during [nitric oxide] inhalation" in patients with LVD. *Id.*

2. INOmax Label (Ex. 1014)

INOmax label contains information provided to medical providers (Ex. 1014 at i) regarding approved iNO uses and contraindications (*id.* at 4, 6). In particular, the reference states that "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." *Id.* at 4. INOmax label warns that the drug "should not be used in the treatment of neonates known to be dependent on right-to-left shunting of blood." *Id.* INOmax label states

that for "Pediatric Use[, n]itric oxide for inhalation has been studied in a neonatal population" (*id.* at 5) and recommends a dose of 20 ppm iNO for neonatal patients with hypoxic respiratory failure (*id.* at 6).

3. Loh (Ex. 1006)

Loh describes a study of the hemodynamic effects of a ten-minute inhalation of nitric oxide (80 ppm) in nineteen adult patients with moderate to severe heart failure due to LVD. Ex. 1006, 2780. Loh further describes measuring the PCWP in the patients studied. *Id.* at 2781.

4. Goyal (Ex. 1007)

Goyal describes a study of the efficacy of inhaled nitroglycerin in reducing pulmonary arterial hypertension in children with congenital heart disease. Ex. 1007, Abstract. During the study, PCWP was measured for all of the patients before and after treatment with inhaled nitroglycerin. *Id.* at 209.

5. Analysis

Petitioner argues that the combination of Bernasconi, INOmax label, Loh, and Goyal teaches or suggests each limitation of the independent claims in the '966 patent, the '284 patent, and the '163 patent. Petitioner also argues that the combination of Bernasconi, Loh, and Goyal teaches or suggests each limitation of independent claims 1, 9, 34, and 37 of the '741 patent. In particular, regarding the exclusion limitations of the claims, Petitioner asserts that Bernasconi discloses that patients with LVD treated with inhaled nitric oxide are at risk of pulmonary edema. -522 Pet. 27 (regarding independent claims 1 and 6 of the '966 patent) (citing Ex. 1004, 8; Ex. 1002 ¶ 38); *see also id.* at 32 (regarding independent claims 13 and 22 of the '966 patent). According to Petitioner, a person of ordinary skill in the art "would have known not to harm patients by administering iNO to

patients at particular risk of developing pulmonary edema." *Id.* at 27 (citing Ex. 1004, 8; Ex. 1002 ¶¶ 24, 34, 38). Petitioner then concludes that a person of ordinary skill in the art "would have known to exclude certain neonates identified as having LVD from iNO treatment." *Id.* (citing Ex. 1004, 8; Ex. 1002 ¶ 38). Petitioner makes the same arguments with respect to the independent claims of the '284 patent and the '163 patent, and independent claims 1, 9, 34, and 37 of the '741 patent. *See* -524 Pet. 25, 30; -525 Pet 23, 28; -526 Pet. 13–25.

We are not persuaded by Petitioner's argument. Bernasconi teaches that there are "several reports of the negative effects of inhaled NO in patients with left ventricular dysfunction." Ex. 1004, 8. Those negative effects include the risk of pulmonary edema. *Id.* But the Specification acknowledges that the risk of pulmonary edema was already known, stating "pulmonary edema has previously been reported with the use of iNO in patients with LVD." Ex. 1001, 13:4–5. And, as Patent Owner notes, despite this knowledge in the art, Bernasconi does not conclude that patients should be excluded from inhaled nitric oxide treatment as a result of a determination that a patient has LVD, as required by the claims. *See* -522 Prelim. Resp. 41. Instead, Bernasconi merely cautions for the "need for careful observation and intensive monitoring *during* NO inhalation in patients with left ventricular failure, if left ventricular afterload is not lowered concomitantly." *See* Ex. 1004, 8 (emphasis added). Thus, contrary to the claim language, Bernasconi teaches that iNO treatment may be given to patients with LVD, as long as those patients are monitored carefully during treatment.

We are also not persuaded that Petitioner has shown sufficiently that the teachings of Bernasconi would suggest to a person of ordinary skill in

the art that *children* with LVD are at an increased risk of pulmonary edema and should, therefore, be excluded from treatment with inhaled nitric oxide. Petitioner's declarant, Dr. Beghetti—who is an author of Bernasconi—states that "the discussion of adverse effects of iNO on patients with LVD is applicable to all patients, including the '[n]eonates with hypoxaemic respiratory failure' addressed in the 'Inhaled nitric oxide applications' section of *Bernasconi*." Ex. 1002 ¶ 36. Dr. Beghetti continues, stating that "the risk of pulmonary oedema resulting from iNO therapy in patients with LVD is a risk in neonates and non-neonates alike." *Id.* Finally, Dr. Beghetti concludes that after reading Bernasconi, evaluating the patient, and weighing the therapeutic benefits of iNO, "one skilled in the art would have understood that certain patients who have left ventricular dysfunction would be at risk of pulmonary oedema, even if not dependent on right-to-left shunting of blood, and should not be treated with inhaled NO." *Id.* ¶ 38.

Dr. Beghetti, however, does not provide any objective support for his opinion that such patients "should not be treated with inhaled NO" (*id.*), particularly when Bernasconi itself taught that treatment with iNO was acceptable, as long as the patient is carefully monitored. We, therefore, do not give persuasive weight to Dr. Beghetti's unsupported opinion. *See* 37 C.F.R. § 42.65(a) (stating opinion testimony that does not disclose underlying facts or data "is entitled to little or no weight"); *Ashland Oil, Inc. v. Delta Resins & Refractories, Inc.*, 776 F.2d 281, 294 (Fed. Cir. 1985) (finding a lack of objective support for expert opinion "may render the testimony of little probative value in a validity determination").

Moreover, Dr. Beghetti provides no persuasive support for his opinion that a person of ordinary skill in the art reading Bernasconi would understand that the risk of pulmonary edema from iNO therapy in patients

with LVD "is a risk in neonates and non-neonates alike." Ex. 1002 ¶ 36. In contrast, Patent Owner provides a number of prior art references that explain that LVD in adults is different than LVD in children, and that state "children are not simply little adults." -522 Prelim. Resp. 30 (citing Ex. 2004, 2; Ex. 1017, 117; Ex. 2009, 1215; Ex. 2010, 5, 8; Ex. 2011, 544; Ex. 2006, 2).

The INOT22 study also provides compelling evidence that the claims are not obvious. As noted above, the Specification acknowledges that it was known in the art that iNO treatment in patients with LVD may cause pulmonary edema. Ex. 1001, 13:6–7. Nevertheless, those patients were not excluded from the original protocol of the study, which, according to the Specification, "was the largest and most rigorous pharmacodynamics study of iNO conducted to date." *Id.* at 13:44–46. We find persuasive Patent Owner's argument and evidence that, if it were obvious to a person of ordinary skill in the art to exclude children with LVD from treatment with iNO, the experts in the field who designed the study—including the named author of the Macrae reference relied on by Petitioner—would have excluded those children from the original protocol. -522 Prelim. Resp. 45, 34.

Finally, during prosecution of the involved patents, the applicants made many of the same arguments that Patent Owner makes in its Preliminary Responses. That is, the applicants argued that studies on adults with LVD, like that described in Loh, could not be extrapolated to results in children, because "LVD in children or neonates is 'drastically different' than LVD in adults." -522 Prelim. Resp. 15–17 (citation omitted). The applicants also argued that the fact that children with LVD were not excluded from the original protocol of the INOT22 study is evidence of nonobviousness. *Id.* at 48. Petitioner, however, does not address any of

these arguments in its Petition, despite including the file history as an exhibit. *See* Ex. 1052. Given the Examiner found these arguments persuasive and allowed the claims, we agree with Patent Owner that Petitioner and its declarant should have addressed these arguments in the Petitions to show a reasonable likelihood of success on the merits.

Accordingly, we find that Petitioner has failed to show sufficiently that the cited art teaches or suggests the exclusion limitation of the claims. Thus, after considering the parties' arguments and evidence, we are not persuaded that Petitioner has established a reasonable likelihood of success that it would prevail in showing any of the claims of the '966 patent, the '284 patent, and the '163 patent are unpatentable as obvious over Bernasconi, INOmax label, Loh, and Goyal, or that claims 1–23, 31, 32, and 34–44 of the '741 patent are unpatentable as obvious over Bernasconi, Loh, and Goyal.

C. Obviousness of the '966 Patent, the '284 Patent, and the '163 Patent Claims over Ichinose, Neonatal Group, Macrae, Loh, Goyal, and Germann

Relying on the testimony of Dr. Beghetti, Petitioner also asserts that each of the independent claims of the '966 patent, the '284 patent, and the '163 patent is unpatentable as obvious over Ichinose, Neonatal Group, Macrae, Loh, Goyal, and Germann. -522 Pet. 41–53. Patent Owner opposes Petitioner's assertion. -522 Prelim. Resp. 53–55. We determine, on the current record, that Petitioner has not established a reasonable likelihood that it would prevail in showing the cited references render any of those challenged claims obvious.

1. Ichinose (Ex. 1009)

Ichinose is a review article disclosing the uses and therapeutic potential of inhaled nitric oxide. Ex. 1009, 3106. Ichinose discusses the

approval of iNO for the treatment of newborns with hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension. *Id.* at 3107–08. Ichinose also states that, although early studies of inhaled nitric oxide to treat pulmonary hypertension used concentrations of 5 to 80 ppm, it has since been recognized that concentrations greater than 20 ppm provide little additional therapeutic benefit in most patients. *Id.* at 3106. Ichinose further states that inhalation of low levels of nitric oxide appears to be safe, but that "it is important to be aware of the possibility that inhaled NO can produce pulmonary vasodilation and may overwhelm a failing [left ventrical], thereby producing pulmonary edema." *Id.* at 3109.

2. Neonatal Group (Ex. 1011)

Neonatal Group describes the results of a randomized, multicenter study to determine whether inhaled nitric oxide would reduce mortality or the initiation of extracorporeal membrane oxygenation in infants with hypoxic respiratory failure. Ex. 1011, Abstract. The study found that nitric oxide therapy reduced the use of extracorporeal membrane oxygenation, but had no apparent effect on mortality in critically ill infants with hypoxic respiratory failure. *Id.*

3. Macrae (Ex. 1008)

Macrae discusses the use of inhaled nitric oxide in neonates and children with cardiorespiratory failure. Ex. 1008, Abstract. Macrae notes that studies of inhaled nitric oxide in term or near-term babies have used echocardiography to exclude patients with congenital heart disease as a cause of hypoxemia. *Id.* at 373–74. For example, Macrae states that inhaled nitric oxide may be harmful to babies with severe LVD with right-to-left ductal shunting. *Id.* at 374.

4. Germann (Ex. 1010)

Germann discloses the use of inhaled nitric oxide to treat acute respiratory failure and pulmonary hypertension in adults. Ex. 1010, Abstract. Germann also provides expert recommendations for the use of inhaled nitric oxide in adults. *Id.* For example, for patients with chronic left ventricular failure, Germann states that some studies report sudden development of pulmonary edema in patients with severe congestive heart failure who were treated with inhaled nitric oxide. *Id.* at 1033. Germann further states that inhaled nitric oxide may be dangerous in patients with LVD. *Id.*

5. Analysis

Petitioner asserts that the combination of Ichinose, Neonatal Group, Macrae, Loh, Goyal, and Germann teaches or suggests each limitation of each of the independent claims of the '966 patent, the '284 patent, and the '163 patent. In particular, for the exclusion limitation of the independent claims of the '966 patent, Petitioner asserts that a person of ordinary skill in the art would have known that "all patients with LVD, ***whether or not*** they depended on right-to-left shunting, were at risk of pulmonary edema if treated with iNO." -522 Pet. 48 (citing Ex. 1009, 3109; Ex. 1002 ¶¶ 61, 67). Petitioner further argues that Ichinose discloses that patients with LVD treated with iNO are at risk of pulmonary edema. *Id.* (citing Ex. 1009, 3109). Moreover, Petitioner asserts that Germann discloses that "treating patients with LVD with iNO may be dangerous," because Germann states that "[i]n the presence of left heart dysfunction it is increasingly recognised that iNO testing should be performed only after optimising heart failure therapy immediately prior to testing." *Id.* at 48–49 (citing Ex. 1010, 1033; Ex. 1002 ¶ 67). Petitioner concludes that a person of ordinary skill in the art

reading Ichinose and Germann would have understood that patients with LVD were at risk of pulmonary edema upon treatment with iNO and "would have evaluated the risks associated with iNO treatment and excluded the patients from iNO treatment." *Id.* at 49 (citing Ex. 1002 ¶¶ 63, 65, 67, 72; Ex. 1009, 3109; Ex. 1010, 1033). Petitioner makes the same arguments with respect to the '284 and '163 patents. -524 Pet. 46–47, 50–51; -525 Pet. 40–41, 44–45.

Patent Owner asserts that both Ichinose and Germann relate to patient populations that are distinct from the claimed excluded group, and Petitioner does not explain why the teachings of those references would be applied by a person of ordinary skill in the art to the claimed excluded group. -522 Prelim. Resp. 54. For example, Patent Owner notes that Germann relates to inhaled nitric oxide therapy in adults, not children. *Id.* at 55; *see* Ex. 1010, Title, Abstract.

Patent Owner also notes that the reference cited by Ichinose as support for the risk of pulmonary edema, Beghetti (1997),[16] was a letter to the editor in response to a case study reported in Henrichsen.[17] Ex. 2004, 844. Henrichsen describes a baby with PPHN and LVD who developed systemic hypotension after exposure to inhaled nitric oxide. Ex. 1030, 183. That baby, however, was dependent on right-to-left shunting of blood, a condition which is expressly excluded from each of the claims. *See id.*; *see, e.g.*, Ex. 1001, claim 1 (performing echocardiography to identify a child in need of iNO "wherein the child is not dependent on right-to-left shunting of

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[16] M. Beghetti et al., Letter to the Editor, *Inhaled Nitric Oxide Can Cause Severe Systemic Hypotension*, 130 J. PEDIATR. 844 (1997) (Ex. 2004).

[17] T. Henrichsen et al., Letter to the Editor, *Inhaled Nitric Oxide Can Cause Severe Systemic Hypotension*, 129 J. PEDIATR. 183 (1996) (Ex. 1030).

blood"). Moreover, when specifically discussing the treatment of newborns, Ichinose states "[l]arge clinical trials have demonstrated that NO inhalation is safe in the hypoxemic term newborn." Ex. 1009, 3108.

After considering both parties' arguments and evidence, we are not persuaded that Petitioner has shown sufficiently that the combination of Ichinose and Germann teaches or suggests the exclusion limitation of the claims, as Petitioner asserts. As explained above, we are not persuaded that Petitioner has shown sufficiently that a person of ordinary skill in the art would reasonably expect that children with LVD would be at risk of SAEs like pulmonary edema from iNO treatment. For example, we are not persuaded that a person of ordinary skill in the art would apply studies regarding iNO treatment in adults to treatment in children. We are, therefore, not persuaded that a person of ordinary skill in the art would apply Germann's teachings for adult iNO treatment to the treatment of children. Similarly, we are not persuaded that a person of ordinary skill in the art would look to Ichinose and its observations with respect to a neonate dependent on right-to-left shunting of blood when such patients are excluded from the claimed methods. Finally, as explained above, we are persuaded by the fact that the experts in the field designing the INOT22 study did not exclude children with LVD from the original protocol.

Accordingly, after considering both parties' arguments and evidence, we are not persuaded that Petitioner has shown a reasonable likelihood that it would prevail in showing that any of the claims of the '966 patent, the '284 patent, and the '163 patent are unpatentable as obvious over Ichinose, Neonatal Group, Macrae, Loh, Goyal, and Germann.

D. Obviousness of Claims 1–23, 31, 32, and 34–44 of the '741 Patent over Ichinose, Neonatal Group, Macrae, Loh, Goyal, and Germann

Petitioner asserts that claims 1–23, 31, 32, and 34–44 of the '741 patent are unpatentable over Ichinose, Neonatal Group, Macrae, Loh, Goyal, and Germann. -526 Pet. 39–54. Regarding the exclusion limitations of independent claims 1, 9, 34, and 37, Petitioner argues that Ichinose discloses that patients with LVD treated with iNO are at risk of pulmonary edema, and that Loh discloses that patients with LVD show an increased wedge pressure upon iNO treatment. *Id.* at 46 (citing Ex. 1009, 3109; Ex. 1006, 2780–81, Table 1). Petitioner further argues that because patients with LVD were at risk of increased wedge pressure and pulmonary edema from iNO treatment, a person of ordinary skill in the art reading Ichinose and Loh "would have considered the benefits and risks of treating such patients with iNO and would have excluded such patients from or discontinued iNO treatment if the risks outweighed the benefits." *Id.*

Patent Owner asserts substantially the same arguments regarding Ichinose that it set forth with respect to the claims of the other involved patents. That is, it argues that Ichinose relates to a neonate dependent on right-to-left shunting of blood, which is "excluded from the '741 claims." -526 Prelim. Resp. 56. Patent Owner also argues that Loh, which was considered by the Examiner during prosecution, is directed to adult patients and has nothing to do with children who have LVD. *Id.* at 43 (citing Ex. 1006, 2780).

After considering both parties' arguments and evidence, we are not persuaded that Petitioner has shown sufficiently that the cited prior art teaches or suggests the exclusion limitations of the claims. As an initial matter, we note that the '741 claims do not expressly exclude children

dependent on right-to-left shunting of blood, as Patent Owner asserts. Regardless, we find persuasive Patent Owner's argument that Petitioner has failed to establish why a person of ordinary skill in the art would apply Loh's teachings relating to adults to the treatment of children. We also find persuasive Patent Owner's argument that the INOT22 study is evidence of nonobviousness, as explained above. Because Petitioner failed to address persuasively either of these arguments—despite the fact that both were raised during prosecution—we determine that Petitioner has not established a reasonable likelihood that it would prevail in showing that claims 1–23, 31, 32, and 34–44 of the '741 patent are unpatentable over Ichinose, Neonatal Group, Macrae, Loh, Goyal, and Germann.

E. Obviousness of Claims 24–30 and 33 of the '741 Patent over Bernasconi, INOmax Label, Loh, Juliana, and Goyal

Petitioner asserts that claims 24–27, 29, 30, and 33 of the '741 patent are unpatentable over Bernasconi, INOmax label, Loh, Juliana, and Goyal. -526 Pet. 54–60. Petitioner further asserts that claim 28, which depends from independent claim 24, is unpatentable over Bernasconi, INOmax label, Loh, Juliana, Macrae, and Goyal. *Id.* at 60. We determine that Petitioner has not established a reasonable likelihood that it would prevail on its assertions.

1. Juliana (Ex. 1010)

Juliana describes a case of a full-term neonate with severe PPHN. Ex. 1010, Abstract. Cardiac ultrasound confirmed a right-to-left shunt through an open arterial duct. *Id.* at 627. The patient was not treated with inhaled nitric oxide because of the high cost of the treatment, but was treated successfully with one dose of sildenafil. *Id.*

2. Analysis

As explained above, we interpret steps (d) and (e) of claim 24 as equivalent to the exclusion limitations of the other challenged claims. For the step of "determining that a second patient . . . has pre-existing left ventricular dysfunction, so is at particular risk of increased PCWP leading to pulmonary edema upon treatment with inhaled nitric oxide" of claim 24(d), Petitioner relies on its arguments with respect claim 1(c). -526 Pet. 34. That is, Petitioner argues that Bernasconi discloses that patients with LVD are at risk of pulmonary edema upon treatment with iNO. *Id.* at 20. Petitioner also argues that Loh discloses that patients with LVD have an increased wedge pressure upon iNO treatment, and that Goyal confirms that it was well known that wedge pressure could be measured in infants. *Id.* at 20–21. For step (e), "administering a second treatment regimen . . . 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," Petitioner relies on Juliana's disclosure that neonates with PPN can be treated with sildenafil instead of inhaled nitric oxide. *Id.* at 34 (citing Ex. 1032, Abstract, 627; Ex. 1002 ¶ 53). Petitioner then concludes that a person of ordinary skill in the art reading Juliana "would have understood to administer a treatment other than iNO, *i.e.,* sildenafil." *Id.* at 34–35.

For the same reasons stated above, we are not persuaded that Petitioner has shown sufficiently that a person of ordinary skill in the art reading Bernasconi and Loh would reasonably expect neonates with LVD to be "at particular risk of increased PCWP leading to pulmonary edema upon treatment with inhaled nitric oxide," as required by claim 24(d). Accordingly, we determine that Petitioner has not established a reasonable

likelihood that it would prevail in showing that claims 24–30 and 33 of the '741 patent are unpatentable over the cited references.

III. CONCLUSION

We conclude that Petitioner has not demonstrated a reasonable likelihood of prevailing on its assertions that claims 1–29 the '966 patent; claims 1–30 of the '284 patent; claims 1–25 of the '163 patent; and claims 1–44 of the '741 patent are unpatentable as obvious.

IV. ORDER

In consideration of the foregoing, it is hereby ordered that the Petitions in IPR2015-00522, IPR2015-00524, IPR2015-00525, and IPR2015-00526 are *denied.*

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