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(71) Applicant (for all designated States except US): **IKARIA HOLDINGS, INC.** [US/US]; 6 Route 173, Chester, NJ 07930 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **BALDASSARRE, James, S.** [US/US]; 145 Pebble Woods Drive, Doylestown, PA 18901 (US). **ROSSKAMP, Ralf** [DE/US]; 1 Byron Court, Chester, NJ 07930 (US).

(74) Agents: **ROGERS, Christopher, P.** et al.; Lee & Hayes, PLLC, 601 W. Riverside Ave, Suite 1400, Spokane, WA 99201 (US).

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(54) Title: METHODS OF IDENTIFYING A PATIENT POPULATION ELIGIBLE FOR TREATMENT WITH NITRIC OXIDE VIA INHALATION

(57) Abstract: The invention relates methods of reducing the risk or preventing the occurrence of an adverse event (AE) or a serious adverse event (SAE) associated with a medical treatment comprising inhalation of nitric oxide.

METHODS OF IDENTIFYING A PATIENT POPULATION ELIGIBLE FOR TREATMENT WITH NITRIC OXIDE VIA INHALATION

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit to U.S. Utility Application Serial No. 5 12/494,598, filed June 30, 2009, entitled "Methods of Treating Term and Near-Term Neonates Having Hypoxic Respiratory Failure Associated with Clinical or Echocardiographic Evidence of Pulmonary Hypertension", which is incorporated herein by reference in their entirety.

10 STATEMENT CONCERNING GOVERNMENT INTEREST

[0002] Not applicable.

BACKGROUND OF THE INVENTION

[0003] INOmax®, (nitric oxide) for inhalation is an approved drug product for the 15 treatment of term and near-term (>34 weeks gestation) neonates having hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension.

[0004] The use of inhaled NO (iNO) has been studied and reported in the literature. (Kieler-Jensen M et al., 1994, Inhaled Nitric Oxide in the Evaluation of Heart Transplant Candidates with Elevated Pulmonary Vascular Resistance, *J Heart Lung Transplantation* 13:366-375; Pearl RG et al., 1983, Acute Hemodynamic Effects of Nitroglycerin in Pulmonary Hypertension, *American College of Physicians* 99:9-13; Ajami GH et al., 2007, Comparison of the Effectiveness of Oral Sildenafil Versus Oxygen Administration as a Test for Feasibility of Operation for Patients with Secondary Pulmonary Arterial Hypertension, *Pediatr Cardiol*; Schulze-Neick I et al., 2003, Intravenous Sildenafil Is a Potent Pulmonary Vasodilator in 25 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).

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SUMMARY OF THE INVENTION

[0005] One aspect of the invention relates to a pre-screening methodology or protocol having exclusionary criteria to be evaluated by a medical provider prior to treatment of a near-term neonate, neonate, child or adult patient with iNO. One objective of the invention is to evaluate and possibly exclude from treatment patients eligible for treatment with iNO, who have 10 pre-existing left ventricular dysfunction (LVD). Patients who have been diagnosed as having 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 15 iNO as a treatment option.

[0006] Accordingly, one aspect of the invention includes a method of reducing the risk or preventing the occurrence, in a near-term neonate, neonate, child or adult 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 20 pharmaceutically acceptable nitric oxide gas to a medical provider; and, (b) informing the medical provider that excluding such patients who have been diagnosed as having pre-existing left ventricular dysfunction from said treatment reduces the risk or prevents the occurrence of the adverse event or the serious adverse event associated with said medical treatment.

[0007] Further provided herein is a method of reducing the risk or preventing the 25 occurrence, in a near-term neonate, neonate, child or adult 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 such patients having pre-existing left ventricular dysfunction experience an increased risk of serious adverse 30 events associated with said medical treatment.

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

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

[0010] In an exemplary embodiment of the method, the method further comprises informing the medical provider that there is a risk associated with using inhaled nitric oxides in a near-term neonate, neonate, child or adult patients who have been diagnosed as having pre-existing or clinically significant left ventricular dysfunction and that such risk should be evaluated on a case by case basis.

[0011] In another exemplary embodiment of the method, the method further comprises informing the medical provider that there is a risk associated with using inhaled nitric oxide in a near-term neonate, neonate, child or adult patient who have been diagnosed as having left ventricular dysfunction.

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

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

[0014] In another exemplary embodiment of the method, the iNO treatment further comprises inhalation of oxygen (O₂) or concurrent ventilation.

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

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

[0017] In another exemplary embodiment of the method, the patient population comprises neonates and near-term neonates.

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

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

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

DETAILED DESCRIPTION OF THE EXEMPLARY EMBODIMENTS

[0021] INOmax® (nitric oxide) for inhalation was approved for sale in the United States by the U.S. Food and Drug Administration (“FDA”) in 1999. Nitric oxide, the active substance in INOmax®, is a selective pulmonary vasodilator that increases the partial pressure of arterial oxygen (PaO₂) by dilating pulmonary vessels in better ventilated areas of the lung, redistributing pulmonary blood flow away from the lung regions with low ventilation/perfusion (V/Q) ratios toward regions with normal ratios. INOmax® significantly improves oxygenation, reduces the need for extracorporeal oxygenation and is indicated to be used in conjunction with ventilatory support and other appropriate agents. The current FDA-approved prescribing information for INOmax® is incorporated herein by reference in its entirety.

[0022] INOmax® is a gaseous blend of NO and nitrogen (0.08% and 99.92% respectively for 800 ppm; and 0.01% and 99.99% respectively for 100 ppm) and is supplied in aluminium cylinders as a compressed gas under high pressure. In general, INOmax® is administered to a patient in conjunction with ventilatory support and O₂. Delivery devices suitable for the safe and effective delivery of gaseous NO for inhalation include the INOvent®, INOmax DS®, INOpulse®, INOblender®, or other suitable drug delivery and regulation devices or components incorporated therein, or other related processes, which are described in various patent documents including USPNs 5,558,083; 5,732,693; 5,752,504; 5,732,694; 6,089,229; 6,109,260; 6,125,846; 6,164,276; 6,581,592; 5,918,596; 5,839,433; 7,114,510; 5,417,950; 5,670,125; 5,670,127; 5,692,495; 5,514,204; 7,523,752; 5,699,790; 5,885,621; US Patent Application Serial Nos. 11/355,670 (US 2007/0190184); 10/520,270 (US 2006/0093681); 11/401,722 (US 2007/0202083); 10/053,535 (US 2002/0155166); 10/367,277 (US 2003/0219496); 10/439,632 (US 2004/0052866); 10/371,666 (US 2003/0219497); 10/413,817 (US 2004/0005367); 12/050,826 (US 2008/0167609); and PCT/US2009/045266, all of which are incorporated herein by reference in their entirety.

[0023] Such devices deliver INOmax® into the inspiratory limb of the patient breathing circuit in a way that provides a constant concentration of NO to the patient throughout the inspired breath. Importantly, suitable delivery devices provide continuous integrated monitoring of inspired O₂, NO₂ and NO, a comprehensive alarm system, a suitable power source for uninterrupted NO delivery and a backup NO delivery capability.

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

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

5 [0026] As used herein, the terms "adverse event" or "AE" (and variations thereof) mean any untoward occurrence in a subject, or clinical investigation subject administered a pharmaceutical product (such as nitric oxide) and which does not necessarily have a causal relationship with such treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporarily 10 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.

15 [0027] As used herein, the terms "adverse drug reaction" or "ADR" (and variations thereof) mean any noxious and unintended response to a medicinal product related to any dose.

20 [0028] As used herein, the terms "serious adverse event" or "SAE" (or "serious adverse drug reaction" or "serious ADR") (and variations thereof) mean a significant hazard or side effect, regardless of the investigator's opinion on the relationship to the investigational product. A serious adverse event or reaction is any untoward medical occurrence that at any dose: results 25 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 30 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.

5 [0029] Left Ventricular Dysfunction. Patients having pre-existing LVD may be described in general as those with elevated pulmonary capillary wedge pressure, including those with diastolic dysfunction (including hypertensive cardiomyopathy), those with systolic dysfunction, including those with cardiomyopathies (including ischemic or viral cardiomyopathy, or idiopathic cardiomyopathy, or autoimmune disease related cardiomyopathy, and side effects due to drug related or toxic-related cardiomyopathy), or structural heart disease, 10 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.

15 [0030] Pulmonary Capillary Wedge Pressure. Pulmonary capillary wedge pressure, or "PCWP", provides an estimate of left atrial pressure. Identifying patients with pre-existing PCWP is known to those skilled in the medicinal arts, and such techniques for example may include measure by inserting balloon-tipped, multi-lumen catheter (also known as a Swan-Ganz catheter). Measure of PCWP may be used as a means to diagnose the severity of LVD 20 (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.

25 [0031] In cardiac physiology, afterload is used to mean the tension produced by a chamber of the heart in order to contract. If the chamber is not mentioned, it is usually assumed to be the left ventricle. However, the strict definition of the term relates to the properties of a single cardiac myocyte. It is therefore only of direct relevance in the laboratory; in the clinic, the term end-systolic pressure is usually more appropriate, although not equivalent.

[0032] The terms "left ventricular afterload" (and variations thereof) refer to the pressure that the chamber of the heart has to generate in order to eject blood out of the chamber. Thus, it is a consequence of the aortic pressure since the pressure in the ventricle must be greater than the systemic pressure in order to open the aortic valve. Everything else held equal, as afterload increases, cardiac output decreases. Disease processes that increase the left ventricular afterload include increased blood pressure and aortic valve disease. Hypertension (Increased blood pressure) increases the left ventricular afterload because the left ventricle has to work harder to eject blood into the aorta. This is because the aortic valve won't open until the pressure generated in the left ventricle is higher than the elevated blood pressure. Aortic stenosis increases the afterload because the left ventricle has to overcome the pressure gradient caused by the stenotic aortic valve in addition to the blood pressure in order to eject blood into the aorta. For instance, if the blood pressure is 120/80, and the aortic valve stenosis creates a trans-valvular gradient of 30 mmHg, the left ventricle has to generate a pressure of 110 mmHg in order to open the aortic valve and eject blood into the aorta. Aortic insufficiency increases afterload because a percentage of the blood that is ejected forward regurgitates back through the diseased aortic valve. This leads to elevated systolic blood pressure. The diastolic blood pressure would fall, due to regurgitation. This would result in an increase pulse pressure. Mitral regurgitation decreases the afterload. During ventricular systole, the blood can regurgitate through the diseased mitral valve as well as be ejected through the aortic valve. This means that the left ventricle has to work less to eject blood, causing a decreased afterload. Afterload is largely dependent upon aortic pressure.

[0033] An intra-aortic balloon pump (IABP) is a mechanical device that is used to decrease myocardial oxygen demand while at the same time increasing cardiac output. By increasing cardiac output it also increases coronary blood flow and therefore myocardial oxygen delivery. It consists of a cylindrical balloon that sits in the aorta and counterpulsates. That is, it actively deflates in systole increasing forward blood flow by reducing afterload thus, and actively inflates in diastole increasing blood flow to the coronary arteries. These actions have the combined result of decreasing myocardial oxygen demand and increasing myocardial oxygen supply. The balloon is inflated during diastole by a computer controlled mechanism, usually linked to either an ECG or a pressure transducer at the distal tip of the catheter; some IABPs, such as the Datascope System 98XT, allow for asynchronous counterpulsation at a set

rate, though this setting is rarely used. The computer controls the flow of helium from a cylinder into and out of the balloon. Helium is used because its low viscosity allows it to travel quickly through the long connecting tubes, and has a lower risk of causing a harmful embolism should the balloon rupture while in use. Intraaortic balloon counterpulsation is used in situations when 5 the heart's own cardiac output is insufficient to meet the oxygenation demands of the body. These situations could include cardiogenic shock, severe septic shock, post cardiac surgery and numerous other situations.

[0034] Patients eligible for treatment with iNO. In general, patients approved for treatment of iNO are term and near-term (>34 weeks gestation) neonates having hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension, a condition also known as persistent pulmonary hypertension in the newborn (PPHN). Due to the selective, non-systemic nature of iNO to reduce pulmonary hypertension, physicians skilled in the art further employ INOmax® to treat or prevent pulmonary hypertension and improve blood O₂ levels in a variety of other clinical settings, including in 10 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 15 preventing or treating reversible pulmonary vasoconstriction, reducing pulmonary arterial pressure and improving pulmonary gas exchange.

[0035] A small proportion of INOmax® sales stem from its use by clinicians in a premature infant population. In these patients, INOmax® is generally utilized by physicians as a rescue therapy primarily to vasodilate the lungs and improve pulmonary gas exchange. Some physicians speculate that INOmax® therapy may promote lung development and/or reduce or 25 prevent the future development of lung disease in a subset of these patients. Although the precise mechanism(s) responsible for the benefits of INOmax® therapy in these patients is not completely understood, it appears that the benefits achieved in at least a majority of these patients are due to the ability of INOmax® to treat or prevent reversible pulmonary vasoconstriction.

[0036] In clinical practice, the use of INOmax® has reduced or eliminated the use of high risk systemic vasodilators for the treatment of PPHN. INOmax®, in contrast to systemic vasodilators, specifically dilates the pulmonary vasculature without dilating systemic blood vessels. Further, iNO preferentially vasodilates vessels of aveoli that are aerated, thus 5 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 10 Nitric Oxide in Persistent Pulmonary Hypertension of the Newborn, in *Acute Respiratory Care of the Neonate: A Self-Study Course*, 2d Ed., Askin DF (ed.), NICU Ink Book Publishers, 1997, pp. 369-378 at 372-73).

[0037] INOmax® also possesses highly desirable pharmacokinetic properties as a lung-specific vasodilator when compared to other ostensibly “pulmonary-specific vasodilators.” For 15 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-20 pulmonary vessels.

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

[0039] CINRG study. (See Davidson et al., March 1998, Inhaled Nitric Oxide for the Early Treatment of Persistent Pulmonary Hypertension of the term Newborn; A Randomized, 25 Double-Masked, Placebo-Controlled, Dose-Response, Multicenter Study; *PEDIATRICS* Vol. 101, No. 3, p. 325).

[0040] This study was a double-blind, randomized, placebo-controlled, multicenter trial of 186 term and near-term neonates with pulmonary hypertension and hypoxic respiratory failure. The primary objective of the study was to determine whether INOmax® would reduce 30 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 $\text{H}_2\text{O}/\text{mm Hg}$ were randomly assigned to receive either 5 20 ppm INOmax® (n=97) or nitrogen gas (placebo; n=89) in addition to their ventilatory support. Patients that exhibited a $\text{PaO}_2 > 60$ mm Hg and a pH < 7.55 were weaned to 5 ppm INOmax® or placebo. The primary results from the CINRG study are presented in Table 4. ECMO was the primary endpoint of the study.

10

Table 1: Summary of Clinical Results from CINRG Study

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

[0041] Significantly fewer neonates in the ECMO group required ECMO, and 15 INOmax® significantly improved oxygenation, as measured by PaO_2 , OI, and alveolar-arterial gradient.

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

[0043] The Neonatal Inhaled Nitric Oxide Study (NINOS) group conducted a double-blind, randomized, placebo-controlled, multicenter trial in 235 neonates with hypoxic respiratory failure. The objective of the study was to determine whether iNO would reduce the occurrence of death and/or initiation of ECMO in a prospectively defined cohort of term or near-term neonates with hypoxic respiratory failure unresponsive to conventional therapy. Hypoxic respiratory failure was caused by meconium aspiration syndrome (MAS; 49%), 20 pneumonia/sepsis (21%), idiopathic primary pulmonary hypertension of the newborn (PPHN;

17%), or respiratory distress syndrome (RDS; 11%). Infants \leq 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 $\text{cm H}_2\text{O}/\text{mmHg}$ 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 5 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.

10

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

15 [0044] Adverse Events from CINRG & NINOS. Controlled studies have included 325 patients on INOmax® doses of 5 to 80 ppm and 251 patients on placebo. Total mortality in the pooled trials was 11% on placebo and 9% on INOmax®, a result adequate to exclude INOmax® mortality being more than 40% worse than placebo.

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

20 [0046] From all controlled studies, at least 6 months of follow-up is available for 278 patients who received INOmax® and 212 patients who received placebo. Among these patients, there was no evidence of an AE of treatment on the need for re-hospitalization, special medical services, pulmonary disease, or neurological sequelae.

[0047] In the NINOS study, treatment groups were similar with respect to the incidence 25 and severity of intracranial hemorrhage, Grade IV hemorrhage, per ventricular leukomalacia, cerebral infarction, seizures requiring anticonvulsant therapy, pulmonary hemorrhage, or gastrointestinal hemorrhage.

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

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Table 3: ADVERSE REACTIONS ON THE CINRG TRIAL

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

[0049] Post-Marketing Experience. The following AEs have been reported as part of 10 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 15 is alphabetical: dose errors associated with the delivery system; headaches associated with environmental exposure of INOmax® in hospital staff; hypotension associated with acute withdrawal of the drug; hypoxemia associated with acute withdrawal of the drug; pulmonary edema in patients with CREST syndrome.

[0050] An analysis of AEs and SAEs from both the CINRG and NINOS studies, in 20 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

5 [0051] The INOT22, entitled "Comparison of supplemental oxygen and nitric oxide for inhalation plus oxygen in the evaluation of the reactivity of the pulmonary vasculature during acute pulmonary vasodilatory testing" was conducted both to access the safety and effectiveness of INOmax® as a diagnostic agent in patients undergoing assessment of pulmonary hypertension (primary endpoint), and to confirm the hypothesis that iNO is selective for the 10 pulmonary vasculature (secondary endpoint).

[0052] During, and upon final analysis of the INOT22 study results, applicants discovered that rapidly decreasing the pulmonary vascular resistance, via the administration of iNO to a patient in need of such treatment, may be detrimental to patients with concomitant, pre-existing LVD. Therefore, a precaution for patients with LVD was proposed to be included 15 in amended prescribing information for INOmax®. Physicians were further informed to consider reducing left ventricular afterload to minimize the occurrence of pulmonary edema in patients with pre-existing LVD.

[0053] In particular, the INOT22 protocol studied consecutive children undergoing cardiac catheterization that were prospectively enrolled at 16 centers in the US and Europe. 20 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 unrepairable) or cardiomyopathy, with pulmonary vascular resistance index (PVRI) > 3 u-m². Later amendments, as discussed herein, added an additional inclusionary criteria of a PCWP less than 20 gmm Hg. Patients were studied under general anaesthesia, or with conscious 25 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 O₂ and NO for inhalation plus O₂ in the evaluation of the reactivity of the pulmonary vasculature during acute pulmonary vasodilator testing. Consecutive children undergoing cardiac catheterization 30 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.

5 [0054] The primary objective was to compare the response frequency with iNO and O₂ vs. O₂ 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 O₂ alone, and the alternate treatment in Period 3. All patients received the iNO and O₂ combination treatment in 10 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.

15 [0055] Results for the intent-to-treat (ITT) population, defined as all patients who were randomized to receive drug, indicated that treatment with NO plus O₂ and O₂ alone significantly increased systemic vascular resistance index (SVRI) (Table 4). The change from baseline for NO plus O₂ was 1.4 Woods Units per meter² (WU·m²) (p = 0.007) and that for O₂ was 1.3 WU·m² (p = 0.004). While the change from baseline in SVRI with NO alone was -0.2 WU·m² (p = 0.899) which demonstrates a lack of systemic effect.

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

	Treatment		
	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)

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

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

Ratio PVRI/SVRI	Treatment		
	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 Value¹	< 0.001	< 0.001	0.002

¹ Wilcoxon Signed Rank Test

Source: INOT22 CSR Table 6.5.1 (ATTACHMENT 2)

5 [0057] All three treatments have a preferential effect on the pulmonary vascular bed, suggesting that all three are selective pulmonary vasodilators. The greatest reduction in the ratio was during treatment with NO plus O₂, possibly due to the decrease in SVRI effects seen with O₂ and NO plus O₂. 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)

Ratio PVRI/SVRI	Treatment		
	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 Value¹	< 0.001	< 0.001	0.006

¹ Wilcoxon Signed Rank Test

Source: INOT22 CSR Table 6.5.2 (ATTACHMENT 3)

5 [0058] NO plus O₂ appeared to provide the greatest reduction in the ratio, suggesting that NO plus O₂ was more selective for the pulmonary vasculature than either agent alone.

[0059] Overview of Cardiovascular Safety. In the INOT22 diagnostic study, all treatments (NO plus O₂, O₂, 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)

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decreased O₂ 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 5 (which limits the period in which such events can be reported). There is technically no time limit in which SAEs are to be reported. So, there were 7 AEs during the study and at least one SAE after the study.

[0060] A total of 4 patients had AEs assessed as being related to study drug. These 10 events included bradycardia, low CO syndrome, ST segment elevation on the ECG, low O₂ 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 15 investigator records an AE, they are required to say if (in their opinion) the event is related to the treatment or not. In this case, 4 of 7 were considered by the investigator to be related to treatment.

[0061] The upper limit of normal PCWP in children is 10-12 mm Hg and 15 mm Hg in 20 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 25 SAE upon administration (e.g., worsening of left ventricular function due to the increased flow of blood through the lungs). Accordingly, the protocol for INOT22 was thereafter amended to exclude patients with a baseline PCWP greater than 20 mm Hg after one patient experienced acute circulatory collapse and died during the study. The value "20 mm Hg" was selected to avoid enrollment of a pediatric population with LVD such that they would be most likely at-risk for these SAEs.

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

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

Table 5: Subjects that died, discontinued or experienced SAEs

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

5 [0063] Two of the 3 fatal SAEs were deemed related to therapy. All 4 non-fatal SAEs were also considered related to therapy. The numbers of patients and events were too small to determine whether risk for SAEs differed by treatment, diagnosis, age, gender or race. At least 10 two patients developed signs of pulmonary edema (subjects 05002 and 02002). This is of interest because pulmonary edema has previously been reported with the use of iNO in patients with LVD, and may be related to decreasing PVRI and overfilling of the left atrium. (Hayward CS et al., 1996, Inhaled Nitric Oxide in Cardiac Failure: Vascular Versus Ventricular Effects, *J Cardiovascular Pharmacology* 27:80-85; Bocchi EA et al., 1994, Inhaled Nitric Oxide Leading to Pulmonary Edema in Stable Severe Heart Failure, *Am J Cardiology* 74:70-72; and, Semigran MJ et al., 1994, Hemodynamic Effects of Inhaled Nitric Oxide in Heart Failure, *J Am Coll Cardiology* 24:982-988).

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

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

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

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

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

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

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

CLAIMS

We Claim:

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

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

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

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

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

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

30 7. The method of any one of claims 1-5, wherein the patient population comprises near-term neonates or neonates.

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

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

10 a. identifying a near-term neonate, neonate or child patient eligible for inhalation of nitric oxide treatment;

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

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

thereby reducing the risk or preventing the occurrence of the adverse event or serious

15 adverse event associated with said medical treatment.

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

20 11. The method of claims 9 or 10, wherein the patients who have pre-existing left ventricular dysfunction have one or more conditions selected from diastolic dysfunction, hypertensive cardiomyopathy, systolic dysfunction, ischemic cardiomyopathy, viral cardiomyopathy, idiopathic cardiomyopathy, autoimmune disease related cardiomyopathy, side effects due to drug-related cardiomyopathy, side effects due to toxin-related cardiomyopathy, 25 structural heart disease, valvular heart disease, congenital heart disease, idiopathic pulmonary arterial hypertension, pulmonary hypertension and cardiomyopathy, or associations thereof.

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

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

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

5 15. The method of claim 9, wherein the patient is a near-term neonate or neonate.

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

10 a. providing pharmaceutically acceptable nitric oxide gas to a medical provider; and,
b. informing the medical provider that excluding such patients who have pre-existing left ventricular dysfunction from said treatment reduces the risk or prevents the occurrence of the adverse event or serious adverse event associated with said medical treatment.

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

18. The method of claim 16, wherein the patient is a near-term neonate or neonate.

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

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

- a. providing pharmaceutically acceptable nitric oxide gas to a medical provider; and,
- b. informing the medical provider that such patients having preexisting left ventricular dysfunction experience an increased rate of serious adverse events associated with said medical treatment.

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

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

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

20 24. A method of reducing one or more adverse events or serious adverse events in an intended patient population comprising near-term neonates, neonates and children in need of being treated with iNO comprising:

- a. identifying a patient eligible for iNO treatment;
- b. evaluating and screening the patient to identify if the patient has pre-existing left ventricular dysfunction; and
- c. excluding from iNO treatment a patient identified as having pre-existing left ventricular dysfunction.

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

- 10 a. identifying a patient in need of receiving inhalation of nitric oxide treatment;
- b. evaluating and screening the patient to identify if the patient has pre-existing left ventricular dysfunction; and
- c. administering the inhalation of nitric oxide if the patient does not have pre-existing left ventricular dysfunction, thereby reducing the risk or preventing the occurrence of the adverse event or significant adverse event associated with the inhalation of nitric oxide treatment.

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

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

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

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

5

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

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2010/038652

A. CLASSIFICATION OF SUBJECT MATTER
 INV. A61K31/21 A61K33/00 A61K45/06 A61P9/08 A61P9/12
 ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, BIOSIS, CHEM ABS Data, EMBASE, PASCAL, SCISEARCH, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>LOH EVAN ET AL: "Cardiovascular Effects of Inhaled Nitric Oxide in patients With Left Ventricular Dysfunction" CIRCULATION, vol. 90, no. 6, 1994, pages 2780-2785, XP002577161 ISSN: 0009-7322 the whole document</p> <p>-----</p> <p style="text-align: center;">-/-</p>	1-30

Further documents are listed in the continuation of Box C.

See patent family annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

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- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
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- *&* document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
23 July 2010	29/07/2010
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Authorized officer Albrecht, Silke

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2010/038652

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	SEMIGRAN MARC J ET AL: "Hemodynamic effects of inhaled nitric oxide in heart failure" JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY, vol. 24, no. 4, 1994, pages 982-988, XP009131903 ISSN: 0735-1097 cited in the application the whole document -----	1-30
X	HAYWARD C S ET AL: "Inhaled nitric oxide in cardiac failure: Vascular versus ventricular effects" JOURNAL OF CARDIOVASCULAR PHARMACOLOGY, vol. 27, no. 1, 1996, pages 80-85, XP009131904 ISSN: 0160-2446 cited in the application the whole document -----	1-30
X	OVODOV ET AL: "Nitric oxide: Clinical applications" SEMINARS IN ANESTHESIA, SAUNDERS, CO, NEW YORK, NY, US LNKD- DOI:10.1053/SA.2000.6785, vol. 19, no. 2, 1 June 2000 (2000-06-01), pages 88-97, XP005426335 ISSN: 0277-0326 page 90, column 1 page 93, column 2 - page 94 -----	1-30
X	HENRICHSEN ET AL: "Inhaled nitric oxide can cause severe systemic hypotension" JOURNAL OF PEDIATRICS, MOSBY-YEAR BOOK, ST. LOUIS, MO, US LNKD- DOI:10.1016/S0022-3476(96)70230-5, vol. 129, no. 1, 1 July 1996 (1996-07-01), page 183, XP022199226 ISSN: 0022-3476 the whole document -----	1-30
X	ADATIA ET AL: "Inhaled nitric oxide and hemodynamic evaluation of patients with pulmonary hypertension before transplantation" JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY, ELSEVIER, NEW YORK, NY, US LNKD- DOI:10.1016/0735-1097(95)00048-9, vol. 25, no. 7, 1 June 1995 (1995-06-01), pages 1656-1664, XP005857183 ISSN: 0735-1097 page 1663, column 1 -----	1-30

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INTERNATIONAL SEARCH REPORT

International application No

PCT/US2010/038652

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>CUJEC BIBIANA ET AL: "Inhaled nitric oxide reduction in systolic pulmonary artery pressure is less in patients with decreased left ventricular ejection fraction" CANADIAN JOURNAL OF CARDIOLOGY, vol. 13, no. 9, 1997, pages 816-824, XP002577162 ISSN: 0828-282X the whole document</p> <p>-----</p>	1-30
X	<p>FINDLAY G P: "Paradoxical haemodynamic response to inhaled nitric oxide" INTERNATIONAL JOURNAL OF INTENSIVE CARE 1998 GB, vol. 5, no. 4, 1998, pages 134-139, XP001536771 ISSN: 1350-2794 the whole document</p> <p>-----</p>	1-30
X	<p>BOCCHI E A ET AL: "Inhaled nitric oxide leading to pulmonary edema in stable severe heart failure" AMERICAN JOURNAL OF CARDIOLOGY, CAHNERS PUBLISHING CO., NEWTON, MA, US LNKD- DOI:10.1016/0002-9149(94)90496-0, vol. 74, no. 1, 1 July 1994 (1994-07-01), pages 70-72, XP023278686 ISSN: 0002-9149 [retrieved on 1994-07-01] cited in the application the whole document</p> <p>-----</p>	1-30