FISH & RICHARDSON P.C.

Frederick P. Fish
1855-1930

W.K. Richardson
1859-1951

Street Address
One Marina Park Drive
Boston, Massachusetts
02210-1878

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

Telephone
617 542-5070

Facsimile
877 769-7945

Web Site
www.fr.com

November 21, 2012

Attorney Docket No.: 26047-0003006/3000-US-0008DIV

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

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WASHINGTON, DC

This application is a divisional 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 divisional 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 on June 22, 2010, which is a continuation of U.S. Application Serial No. 12/494,598, filed June 30, 2009, and now abandoned.

Inventor(s): JAMES S. BALDASSARRE AND RALF ROSSKAMP

Title: METHODS OF DISTRIBUTING A PHARMACEUTICAL PRODUCT COMPRISING NITRIC OXIDE GAS FOR INHALATION

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	$250
Excess claim fee	$620
Total Filing fee	$7360

The fees totaling $7360 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.

Direct all correspondence to the following:

94169
PTO Customer Number

Respectfully submitted,

/Janis K. Fraser/

Janis K. Fraser, Ph.D., J.D.
Reg. No. 34,819
Enclosures
JKF/nab
22918954.doc

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Respectfully submitted,

/Janis K. Fraser/

Janis K. Fraser, Ph.D., J.D.
Reg. No. 34,819
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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:	26047-0003006
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
Independent claims in excess of 3	1201	1	250	250

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous-Filing:				
Publ. Fee- early, voluntary, or normal	1504	1	300	300
Processing Fee, except for Provis. apps	1808	1	130	130
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Miscellaneous:				
		Total in USD ($)		**7360**

Electronic Acknowledgement Receipt	
EFS ID:	14288415
Application Number:	13683236
International Application Number:	
Confirmation Number:	5655
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:	26047-0003006
Receipt Date:	21-NOV-2012
Filing Date:	
Time Stamp:	13:51:19
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$7360
RAM confirmation Number	1615
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_0003006.pdf	139133 d4215eb01f2893dfd9f66ee1b08db548e896510d	no	1
Warnings:					
Information:					
2		26047_0003006application.pdf	240216 0b91ea37e1d934ece656254fa729d84b8ffc89f1	yes	30
	Multipart Description/PDF files in .zip description				
	Document Description		**Start**	**End**	
	Specification		1	22	
	Claims		23	29	
	Abstract		30	30	
Warnings:					
Information:					
3	Application Data Sheet	ADS26047_0003006.pdf	1396085 0531e825f6ac910b9b70be0362d6aa28c642c6b5	no	6
Warnings:					
Information:					
4	Oath or Declaration filed	declaration26047_0003006.pdf	120793 04d63cf9b65d8bb5e3b99508b42a4628f290c89f	no	3
Warnings:					
Information:					
5	Power of Attorney	power003006.pdf	4309982 edb1638cc470119a5054d45d8bc07332f29b481b	no	86
Warnings:					
Information:					
6	Transmittal of New Application	papltr26047_0003006.pdf	93940 1b80928fd717640e49699996e6e0db553f038e30	no	2
Warnings:					
Information:					
7	Fee Worksheet (SB06)	fee-info.pdf	43406 07cc409cf1f710f31bcc3afa4b601902176ad70c	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	6343555		

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 OF DISTRIBUTING A PHARMACEUTICAL PRODUCT COMPRISING NITRIC OXIDE GAS FOR INHALATION		

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.

22918943.doc

METHODS OF DISTRIBUTING A PHARMACEUTICAL PRODUCT COMPRISING NITRIC OXIDE GAS FOR INHALATION

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application is a divisional 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 divisional 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 ≤ 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 distributing a pharmaceutical product, the method comprising:

providing a source of nitric oxide gas to a medical provider;

informing the medical provider that a recommended dose of inhaled nitric oxide gas for treatment of neonates with hypoxic respiratory failure is 20 ppm nitric oxide;

providing a first warning to the medical provider that inhaled nitric oxide is contraindicated in the treatment of neonates dependent on right-to-left shunting of blood; and

providing a second warning to the medical provider, distinct from the first warning, that in patients with pre-existing left ventricular dysfunction, inhaled nitric oxide may increase pulmonary capillary wedge pressure (PCWP) leading to pulmonary edema, the second warning being sufficient to cause a medical provider considering inhaled nitric oxide treatment for a plurality of neonatal patients who (a) are suffering from a condition for which inhaled nitric oxide is indicated, and (b) have pre-existing left ventricular dysfunction, to elect to avoid treating one or more of the plurality of patients with inhaled nitric oxide in order to avoid putting the one or more patients at risk of pulmonary edema.

2. The method of claim 1, further comprising generating the source of nitric oxide gas prior to providing the source to the medical provider.

3. The method of claim 2, wherein the source of nitric oxide gas is a gaseous blend of nitric oxide and nitrogen.

4. The method of claim 1, further comprising generating the source of nitric oxide gas by a method comprising compressing nitric oxide and nitrogen gases under high pressure, prior to providing the source to the medical provider.

5. The method of claim 1, wherein the source of nitric oxide gas is a gaseous blend of nitric oxide and nitrogen provided as a compressed gas in a cylinder under high pressure.

6. The method of claim 1, wherein the dose recommendation and the first and second warnings appear in prescribing information supplied with the source of nitric oxide gas.

7. The method of claim 1, wherein, following provision of the source of nitric oxide gas and the first and second warnings to the medical provider, the medical provider:

performs at least one diagnostic process to identify a neonate patient who has hypoxic respiratory failure and is a candidate for 20 ppm inhaled nitric oxide treatment, wherein the neonate patient is not dependent on right to left shunting of blood;

determines that the neonate patient has left ventricular dysfunction; and

evaluates the potential benefit of treating the neonate patient with 20 ppm inhaled nitric oxide vs. the potential risk described in the second warning that inhaled nitric oxide could cause an increase in PCWP leading to pulmonary edema in patients who have left ventricular dysfunction, in order to arrive at a decision of whether or not to treat the neonate patient with inhaled nitric oxide.

8. The method of claim 1, wherein, following provision of the source of nitric oxide gas and the first and second warnings to the medical provider, the medical provider:

perform at least one diagnostic process to identify a plurality of neonate patients who have hypoxic respiratory failure and are candidates for inhaled nitric oxide treatment, wherein the patients of the plurality are not dependent on right to left shunting of blood;

determines prior to treatment with inhaled nitric oxide whether or not each patient of the plurality has left ventricular dysfunction; and

for each patient of the plurality determined to have left ventricular dysfunction, evaluates on a case-by-case basis the potential benefit of treating the patient with 20 ppm inhaled nitric oxide vs. the potential risk described in the second warning that inhaled nitric oxide could cause an increase in PCWP leading to pulmonary edema.

9. The method of claim 7, wherein the dose recommendation and the first and second warnings appear in prescribing information supplied with the source of nitric oxide gas.

10. The method of claim 8, wherein the dose recommendation and the first and second warnings appear in prescribing information supplied with the source of nitric oxide gas.

11. A method of distributing a pharmaceutical product, the method comprising:

providing a source of nitric oxide gas to a medical provider;

informing the medical provider that a recommended dose of inhaled nitric oxide gas for treatment of neonates with hypoxic respiratory failure is 20 ppm nitric oxide;

providing a first warning to the medical provider that inhaled nitric oxide is contraindicated in the treatment of neonates dependent on right-to-left shunting of blood; and

providing a second warning to the medical provider, distinct from the first warning, that in patients with pre-existing left ventricular dysfunction, inhaled nitric oxide may increase PCWP leading to pulmonary edema, the second warning being sufficient to cause a medical provider considering inhaled nitric oxide treatment for a plurality of neonatal patients who (a) are suffering from a condition for which inhaled nitric oxide is indicated, and (b) have pre-existing left ventricular dysfunction, to evaluate (i) the potential benefit of treating the neonatal patients with 20 ppm inhaled nitric oxide vs. (ii) the potential risk that the 20 ppm inhaled nitric oxide could cause pulmonary edema in the neonatal patients due to the patients' left ventricular dysfunction, and accordingly elect to avoid treating one or more of the neonatal patients with inhaled nitric oxide in order to avoid putting the one or more neonatal patients at risk of pulmonary edema.

12. The method of claim 11, further comprising generating the source of nitric oxide gas, prior to providing the source to the medical provider.

13. The method of claim 12, wherein the source of nitric oxide gas is a gaseous blend of nitric oxide and nitrogen.

14. The method of claim 11, further comprising generating the source of nitric oxide gas by a method comprising compressing nitric oxide and nitrogen gases under high pressure, prior to providing the source to the medical provider.

15. The method of claim 11, wherein the source of nitric oxide gas is a gaseous blend of nitric oxide and nitrogen provided as a compressed gas in a cylinder under high pressure.

16. The method of claim 11, wherein the dose recommendation and the first and second warnings appear in prescribing information supplied with the source of nitric oxide gas.

17. The method of claim 11, wherein, following provision of the source of nitric oxide gas and the first and second warnings to the medical provider, the medical provider:

performs at least one diagnostic process to identify a neonatal patient who has hypoxic respiratory failure and is a candidate for inhaled nitric oxide treatment, wherein the neonatal patient is not dependent on right to left shunting of blood;

determines prior to treatment with inhaled nitric oxide that the neonatal patient has left ventricular dysfunction; and

evaluates the potential benefit of treating the neonatal patient with 20 ppm inhaled nitric oxide vs. the potential risk described in the second warning that inhaled nitric oxide could cause an increase in PCWP leading to pulmonary edema in patients who have left ventricular dysfunction, in order to arrive at a decision of whether or not to treat the neonatal patient with inhaled nitric oxide.

18. The method of claim 11, wherein, following provision of the source of nitric oxide gas and the first and second warnings to the medical provider, the medical provider:

performs at least one diagnostic process to identify a plurality of neonatal patients who have hypoxic respiratory failure and are candidates for inhaled nitric oxide treatment, wherein the patients of the plurality are not dependent on right to left shunting of blood;

determines prior to treatment with inhaled nitric oxide whether or not each patient of the plurality has left ventricular dysfunction; and

for each patient of the plurality determined to have left ventricular dysfunction, evaluates on a case-by-case basis the potential benefit of treating the patient with 20 ppm inhaled nitric oxide vs. the potential risk described in the second warning that inhaled nitric oxide could cause an increase in PCWP leading to pulmonary edema.

19. The method of claim 17, wherein the dose recommendation and the first and second warnings appear in prescribing information supplied with the source of nitric oxide gas.

20. The method of claim 18, wherein the dose recommendation and the first and second warnings appear in prescribing information supplied with the source of nitric oxide gas.

21. A method of distributing a pharmaceutical product, the method comprising:

providing a source of nitric oxide gas to a medical provider;

informing the medical provider that a recommended dose of inhaled nitric oxide gas for treatment of neonates with hypoxic respiratory failure is 20 ppm nitric oxide;

providing a first warning to the medical provider that inhaled nitric oxide is contraindicated in the treatment of neonates dependent on right-to-left shunting of blood;

providing a second warning to the medical provider, distinct from the first warning, stating that patients who have pre-existing left ventricular dysfunction and are treated with inhaled nitric oxide may experience pulmonary edema, and recommending that, if pulmonary edema occurs in a patient who has pre-existing left ventricular dysfunction and is treated with inhaled nitric oxide, the treatment with inhaled nitric oxide should be discontinued.

22. The method of claim 21, further comprising generating the source of nitric oxide gas prior to providing it to the medical provider.

23. The method of claim 22, wherein the source of nitric oxide is a compressed gas that is a blend of nitric oxide and nitrogen.

24. The method of claim 21, further comprising generating the source of nitric oxide gas by a method comprising compressing nitric oxide and nitrogen gases under high pressure, prior to providing the source to the medical provider.

25. The method of claim 21, wherein the dose recommendation and the first and second warnings appear in prescribing information supplied with the source of nitric oxide gas.

26. The method of claim 21, wherein, following provision of the source of nitric oxide gas and the first and second warnings to the medical provider, the medical provider:

performs at least one diagnostic process to identify a neonatal patient who is a candidate for inhaled nitric oxide treatment;

determines prior to treatment with inhaled nitric oxide that the neonatal patient is not dependent on right to left shunting of blood, but does have left ventricular dysfunction consistent with a pulmonary capillary wedge pressure greater than or equal to 20 mm Hg;

treats the neonatal patient with 20 ppm inhaled nitric oxide, whereupon the patient experiences pulmonary edema; and

follows the recommendation in the second warning to discontinue the treatment with inhaled nitric oxide due to the patient's pulmonary edema.

27. A method of distributing a pharmaceutical product, the method comprising:

providing a source of nitric oxide gas to a medical provider;

informing the medical provider that a recommended dose of inhaled nitric oxide gas for treatment of neonates is 20 ppm nitric oxide;

providing a first warning to the medical provider that inhaled nitric oxide is contraindicated in the treatment of neonates dependent on right-to-left shunting of blood;

providing a second warning to the medical provider, distinct from the first warning, stating that patients who have pre-existing left ventricular dysfunction and are treated with inhaled nitric oxide may experience hypotension, and recommending that, if hypotension occurs in a patient who has pre-existing left ventricular dysfunction and is treated with inhaled nitric oxide, the treatment with inhaled nitric oxide should be discontinued.

28. The method of claim 27, further comprising generating the source of nitric oxide gas prior to providing the source to the medical provider.

29. The method of claim 27, further comprising generating the source of nitric oxide gas by a method comprising compressing nitric oxide and nitrogen gases under high pressure, prior to providing the source to the medical provider.

30. The method of claim 27, wherein, following provision of the source of nitric oxide gas and the first and second warnings to the medical provider, the medical provider:

performs echocardiography to identify a neonate patient who is a candidate for inhaled nitric oxide treatment;

determines prior to treatment with inhaled nitric oxide that the neonate patient is not dependent on right to left shunting of blood, but does have left ventricular dysfunction consistent with a pulmonary capillary wedge pressure greater than or equal to 20 mm Hg;

treats the neonate patient with 20 ppm inhaled nitric oxide, whereupon the patient experiences hypotension; and

follows the recommendation in the second warning to discontinue the treatment with inhaled nitric oxide due to the patient's hypotension.

ABSTRACT

Disclosed are methods of distributing a pharmaceutical product comprising nitric oxide gas for inhalation.

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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	26047-0003006
	Application Number	
Title of Invention	METHODS OF DISTRIBUTING A PHARMACEUTICAL PRODUCT COMPRISING NITRIC OXIDE GAS FOR INHALATION	

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

Inventor Information:

Inventor 1 Remove

Legal Name

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

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

City	Doylestown	State/Province	PA	Country of Residence i	US

Mailing Address of Inventor:

Address 1	145 Pebble Woods Drive
Address 2	

City	Doylestown	State/Province	PA
Postal Code	18901	Country i	US

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 i	US

Mailing Address of Inventor:

Address 1	1 Byron Court
Address 2	

City	Chester	State/Province	NJ
Postal Code	07930	Country i	US

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Correspondence Information:

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For further information see 37 CFR 1.33(a).

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	26047-0003006
	Application Number	
Title of Invention	METHODS OF DISTRIBUTING A PHARMACEUTICAL PRODUCT COMPRISING NITRIC OXIDE GAS FOR INHALATION	

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Application Information:

Title of the Invention	METHODS OF DISTRIBUTING A PHARMACEUTICAL PRODUCT COMPRISING NITRIC OXIDE GAS FOR INHALATION		
Attorney Docket Number	26047-0003006	**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.

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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)
	Division of	12820866	2010-06-22

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	26047-0003006
	Application Number	
Title of Invention	METHODS OF DISTRIBUTING A PHARMACEUTICAL PRODUCT COMPRISING NITRIC OXIDE GAS FOR INHALATION	

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)
	Division 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

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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).

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

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Authorization to Permit Access:

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

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	26047-0003006
	Application Number	
Title of Invention	METHODS OF DISTRIBUTING A PHARMACEUTICAL PRODUCT COMPRISING NITRIC OXIDE GAS FOR INHALATION	

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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:

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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.

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(•) 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. [X]

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	

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	26047-0003006
	Application Number	
Title of Invention	METHODS OF DISTRIBUTING A PHARMACEUTICAL PRODUCT COMPRISING NITRIC OXIDE GAS FOR INHALATION	

Email Address	

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

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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.

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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.

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 OF DISTRIBUTING A PHARMACEUTICAL PRODUCT COMPRISING NITRIC OXIDE GAS FOR INHALATION		

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 divisional 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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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:

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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.

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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.

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LEGAL NAME OF INVENTOR

Inventor: James S. Baldassarre Date (Optional): October 8, 2012

Signature: /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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I hereby appoint:

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Assignee Name and Address:

INO Therapeutics LLC
Perryville III, Corporate Park
53 Frontage Road, 3rd Floor
Hampton, NJ 08827-9001

A copy of this form, together with a statement under 37 CFR 3.73(c) (Form PTO/SB/96 or equivalent) is required to be filed in each application in which this form is used. The statement under 37 CFR 3.73(c) may be completed by one of the practitioners appointed in this form, and must identify the application in which this Power of Attorney is to be filed.

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		

PTO/AIA/96 (08-12)
Approved for use through 01/31/2013. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

STATEMENT UNDER 37 CFR 3.73(c)

Applicant/Patent Owner: INO Therapeutics LLC

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

Titled: METHODS OF DISTRIBUTING A PHARMACEUTICAL PRODUCT COMPRISING NITRIC OXIDE GAS FOR INHALATION

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
1. From: and Ralf Rosskamp To: Ikaria Holdings, Inc.
The document was recorded in the United States Patent and Trademark Office at
Reel _____, Frame _____, or for which a copy thereof is attached.

2. From: Ikaria Holdings, Inc. To: Ikaria, Inc.
The document was recorded in the United States Patent and Trademark Office at
Reel _____ Frame _____, or for which a copy thereof is attached.

PTO/AIA/96 (08-129)
Approved for use through 01/31/2013. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

STATEMENT UNDER 37 CFR 3.73(c)

3. From: Ikaria, Inc. To: INO Therapeutics LLC

The document was recorded in the United States Patent and Trademark Office at
Reel _____, Frame ____, or for which a copy thereof is attached.

4. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at
Reel _____, Frame_____, or for which a copy thereof is attached.

5. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at
Reel _____, Frame _____, or for which a copy thereof is attached.

6. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at
Reel _____, Frame _____, or for which a copy thereof is attached.

☐ Additional documents in the chain of title are listed on a supplemental sheet(s).

☒ As required by 37 CFR 3.73(c)(1)(i), the documentary evidence of the chain of title from the original owner to the assignee was, or concurrently is being, submitted for recordation pursuant to 37 CFR 3.11.

[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.

Signature	11/21/12 Date
Janis K. Fraser, Ph.D., J.D. Printed or Typed Name	Attorney for assignee Reg. No. 34,819 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

Assignors:

James S. Baldassarre
145 Pebble Woods Drive
Doylestown, PA 18901

Ralf Rosskamp
1 Byron Court
Chester, NJ 07930

Assignee:

Ikaria Holdings, Inc.
6 Route 173
Clinton, NJ 08809

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

100477026

AUTHENTICATION: 7979373

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.

(c) 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 1 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.

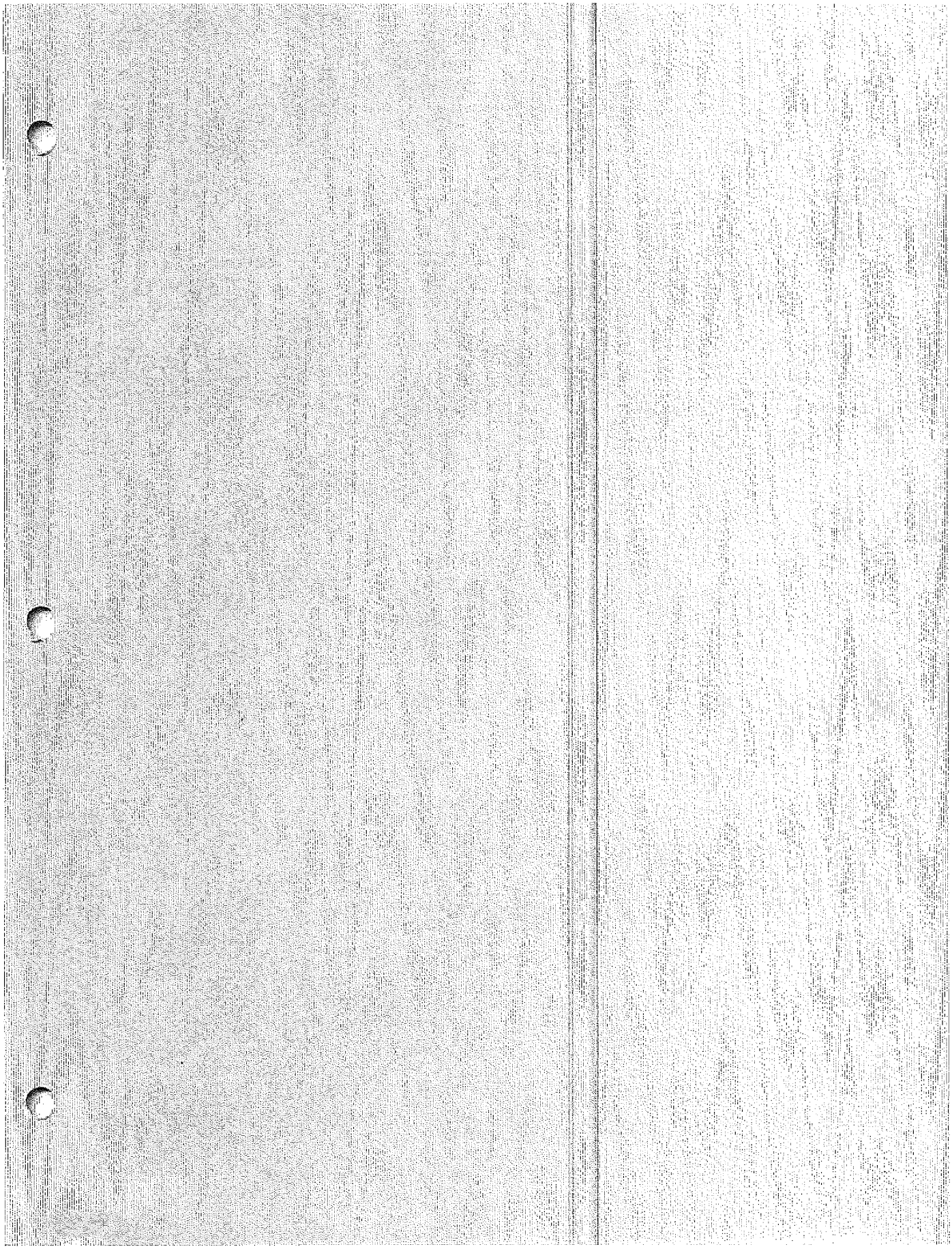
"Trading Day" means a day on which the principal national securities exchange on which the Common Stock is quoted, listed or admitted to trading is open for the transaction of business.

(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.

(c) 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, N.J.
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

PTO/SB/08a (01-10)
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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	13683236
	Filing Date	2012-11-21
	First Named Inventor	Baldassarre
	Art Unit	
	Examiner Name	
	Attorney Docket Number	26047-0003006

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	2	6063407		2000-05-16	Zapol et al.	
	3	6601580		2003-08-05	Bloch et al.	
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	3	20090029371		2009-01-29	Elliot	
	4	20090149541		2009-06-11	Stark et al.	
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	2	WO2005004884	WO		2005-01-20			☐
	3	WO2006127907	WO		2006-11-30			☐
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	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	☐
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	10	Barrington et al., "Inhaled Nitric Oxide for Preterm Infants: A Systematic Review," Pediatrics, Vol. 120; pages 1088-1099, DOI: 10.1542/peds (2007)	☐
	11	Barst et al., "Nitric Oxide in Combination with Oxygen versus Either Oxygen Alone or Nitric Oxide Alone for Acute Vasodilator Testing in Children with Pulmonary Hypertension: A Multicenter, Randomized Study," INO Therapeutics/ Ikaria, Baltimore Convention Center, May 3, 2009, 2 pages, Abstract, downloaded 7/2/2009 from http://127.0.0.1:9080/PAS09A1/view.y?nu=PAS09L1_1507	☐

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	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)	☐
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	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)	☐
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	21	Bloch et al., Cardiovasc. Res. 2007, "Inhaled NO as a therapeutic agent," Vol. 75(2), pages 339-348 (July 15, 2007)	☐
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	23	Bolooki, Clinical Application of the Intra-Aortic Balloon Pump, 3rd Ed., pages 252-253 (1998)	☐
	24	Branson, "Inhaled Nitric Oxide in Adults," The Science Journal of the American Association for Respiratory Care 1997 Open Forum Abstracts, December 7, 1997, 2 pages, retrieved at <<http://www.rcjournal.com/abstracts/1997/?id=A00000929>> on 12/22/2010	☐
	25	Braunwald, Heart Failure, chapter 233 of Harrison's Principles of Internal Medicine, 14th Edition, pages1287-1291 and 1360 (1998)	☐
	26	Bublik et al., "Pediatric cardiomyopathy as a chronic disease: A perspective on comprehensive care programs, Progress in Pediatric," Pediatric Cardiology, Vol. 25, pages 103-111 (2008)	☐
	27	Budts et al., "Residual pulmonary vasoreactivity to inhaled nitric oxide in patients with severe obstructive pulmonary hypertension and Eisenmenger syndrome," Heart, Vol. 86, pages 553-558 (2001)	☐
	28	Canadian Office Action mailed May 31, 2011 for Canadian Patent Application No. 2671029, a counterpart foreign application of US application no. 12/494,598	☐
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	32	Comparison of Supplemental Oxygen and Nitric Oxide for Inhalation in the Evaluation of the Reactivity of the Pulmonary Vasculature During Acute Pulmonary Vasodilator Testing, http://clinicaltrials.gov/archive/NCT00626028/2009_01_12 January 12, 2009	☐
	33	Cornfield et al., "Randomized, Controlled Trial of Low-dose Inhaled Nitric Oxide in the Treatment of Term and Near-term Infants With Respiratory Failure and Pulmonary Hypertension," Pediatrics, Vol. 104, No. 5, pages 1089-1094 (1999)	☐

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	34	Cox et al., "Factors Associated with Establishing a Causal Diagnosis for Children with Cardiomyopathy," Pediatrics, Vol. 118, No 4, pages 1519-1531 (2006)	☐
	35	Cujec 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(9), pages 816-824 (1997)	☐
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	38	Davidson et al., "Safety of Withdrawing Inhaled Nitric Oxide Therapy in Persistent Pulmonary Hypertension of the Newborn," Pediatrics, Vol. 104, No. 2, pages 231-236 (1999)	☐
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	41	Delivery of Inhaled Nitric Oxide Therapy through an Adult or Pediatric Nasal Cannula, Reference: UTMB RESPIRATORY CARE SERVICES Reviewed: 05/31/05	☐
	42	Dickstein et al., "A Theoretic Analysis of the Effect of Pulmonary Vasodilation on Pulmonary Venous Pressure: Implications for Inhaled Nitric Oxide Therapy," The Journal of Heart and Lung Transplant, pages 715-721 (1996)	☐
	43	Dorland, "The American Illustrated Medical Dictionary," 7th edition, W.B. Saunders Company, page 113 (1914)	☐
	44	Dorling, "Neurodevelopmental outcome following Nitric Oxide Therapy for Persistent Pulmonary Hypertension in Term Newborn Infants," Neonatal Intensive Care Unit, Leicester Royal Infirmary, 8/8/2003, modified 11/12/2003, 3 pages	☐

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	45	Douwes et al., "The Maze of Vasodilator Response Criteria," Published online: 26 November 2010, Pediatr. Cardiol., Vol. 32, pages 245-246 (2011)	☐
	46	Ehrenkranz, "Inhaled Nitric Oxide in Full-Term and Nearly Full-Term Infants with Hypoxic Respiratory Failure," The Neonatal Inhaled Nitric Oxide Study Group, N. Engl. J. Med., Vol. 336, No. 9, pages 597-605 (1997)	☐
	47	http://www.cc.nih.gov/ccmd/clinical_services.html, page last updated May 19, 2011	☐
	48	http://www.medterms.com/script/main/art.asp?articlekey=17824, Definition of Contraindication, last Editorial Review March 19, 2012	☐
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	Art Unit	
	Examiner Name	
	Attorney Docket Number	26047-0003006

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

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

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☐ See attached certification statement.

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

☒ A certification statement is not submitted herewith.

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

Signature	/Janis K. Fraser/	Date (YYYY-MM-DD)	2012-11-30
Name/Print	Janis K. Fraser	Registration Number	34819

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International Application Number:	
Confirmation Number:	5655
Title of Invention:	METHODS OF DISTRIBUTING A PHARMACEUTICAL PRODUCT COMPRISING NITRIC OXIDE GAS FOR INHALATION
First Named Inventor/Applicant Name:	James S. Baldassarre
Customer Number:	94169
Filer:	Janis K. Fraser/Nancy Bechet
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Attorney Docket Number:	26047-0003006
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	: James S. Baldassarre et al.	Art Unit	: Unknown
Serial No.	: 13/683,236	Examiner	: Unknown
Filed	: November 21, 2012		
Title	: METHODS OF DISTRIBUTING A PHARMACEUTICAL PRODUCT COMPRISING NITRIC OXIDE GAS FOR INHALATION		

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FIRST 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 12/820,041. The listed references are U.S. patents or US patent application publications, or were submitted or otherwise made of record in application serial no. 12/820,841, 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: November 30, 2012

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

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Applicant	: James S. Baldassarre et al.	Art Unit	: Unknown
Serial No.	: 13/683,236	Examiner	: Unknown
Filed	: November 21, 2012	Conf. No.	: 5655
Title	: METHODS OF DISTRIBUTING A PHARMACEUTICAL PRODUCT COMPRISING NITRIC OXIDE GAS FOR INHALATION		

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This statement supersedes the statement filed earlier today, as the latter inadvertently misidentified the parent application.

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 are U.S. patents or US patent application publications, or were submitted or otherwise made of record in application serial no. 12/821,041, so are not provided with this filing.

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Application Number:	13683236
International Application Number:	
Confirmation Number:	5655
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99)**		
	Application Number	13683236
	Filing Date	2012-11-21
	First Named Inventor	Baldassarre
	Art Unit	
	Examiner Name	
	Attorney Docket Number	26047-0003006

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	6	Federal Regulations 21 CFR Part 312, <<http://www.gcrc.uci.edu/rsa/aer.cfm>>	☐
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	Attorney Docket Number	26047-0003006

	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)	☐
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	Art Unit	
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	Attorney Docket Number	26047-0003006

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☐ 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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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

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EFS ID:	14366831
Application Number:	13683236
International Application Number:	
Confirmation Number:	5655
Title of Invention:	METHODS OF DISTRIBUTING A PHARMACEUTICAL PRODUCT COMPRISING NITRIC OXIDE GAS FOR INHALATION
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:	26047-0003006
Receipt Date:	03-DEC-2012
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Application Type:	Utility under 35 USC 111(a)

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Applicant	: James S. Baldassarre et al.	Art Unit	: Unknown
Serial No.	: 13/683,236	Examiner	: Unknown
Filed	: November 21, 2012		
Title	: METHODS OF DISTRIBUTING A PHARMACEUTICAL PRODUCT COMPRISING NITRIC OXIDE GAS FOR INHALATION		

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Respectfully submitted,

Date: December 3, 2012

/Janis K. Fraser/
Janis K. Fraser, Ph.D., J.D.
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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)	☐
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	Examiner Name	
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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	☐
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Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

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Signature	/Janis K. Fraser/	Date (YYYY-MM-DD)	2012-12-04
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EFS ID:	14378551
Application Number:	13683236
International Application Number:	
Confirmation Number:	5655
Title of Invention:	METHODS OF DISTRIBUTING A PHARMACEUTICAL PRODUCT COMPRISING NITRIC OXIDE GAS FOR INHALATION
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:	26047-0003006
Receipt Date:	04-DEC-2012
Filing Date:	21-NOV-2012
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Application Type:	Utility under 35 USC 111(a)

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1	Transmittal Letter	IDSTHIRD0003006.pdf	62929 e59c9b9ed8da1d99d28d993112b865e05132c3a5	no	1

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Applicant	: James S. Baldassarre et al.	Art Unit	: Unknown
Serial No.	: 13/683,236	Examiner	: Unknown
Filed	: November 21, 2012	Conf. No.	: 5655
Title	: METHODS OF DISTRIBUTING A PHARMACEUTICAL PRODUCT COMPRISING NITRIC OXIDE GAS FOR INHALATION		

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Respectfully submitted,

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/Janis K. Fraser/
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	34	Translated copy of the Japanese Office Action mailed February 15, 2011 for Japanese Patent Application No.2009-157623, a counterpart foreign application for US Patent Application No. 12/494,598	☐
	35	Troncy et al. "Inhaled nitric oxide: clinical applications, indications, and toxicology," Can. J. Anaesth, Vol. 44 (9), pages 972-988 (1997)	☐
	36	UCI General Clinical Research Center, Federal Regulations 21 CFR Part 312, <<http://www.gcrc.uci.edu/rsa/aer.cfm>>, retrieved 9/13/2010, 2 pages	☐
	37	University of Alabama, NCT00732537 at Clinicaltrials.gov (2008)	☐
	38	"Use of Inhaled Nitric Oxide," American Academy of Pediatrics - Committee on Fetus and Newborn, Pediatrics Vol. 106, No. 2, pages 344-345 (2000)	☐
	39	UTMB Respiratory Care Services, "Delivery of Inhaled Nitric Oxide Therapy through an Adult or Pediatric Nasal Cannula," 4 pages, (2003)	☐
	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)	☐
	43	Weinberger et al., "Nitric Oxide in the lung: therapeutic and cellular mechanisms of action", Pharmacology & Therapeutics, Vol. 84, pages 401-411 (1999)	☐
	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)	☐

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	13683236
	Filing Date	2012-11-21
	First Named Inventor	Baldassarre
	Art Unit	
	Examiner Name	
	Attorney Docket Number	26047-0003006

	45	Wessel et al., "Managing low cardiac output syndrome after congenital heart surgery," Crit. Care Med., Vol. 29(10) pages S220-S230 (2001)	☐
	46	Wheeler et al., "The Central Nervous System in Pediatric Critical Illness and Injury," Pediatric Critical Care Medicine, Springer, page 278 (2007)	☐
	47	Wilkinson et al., "Epidemiological and outcomes research in children with pediatric cardiomyopathy; discussions from the international workshop on primary and idiopathic cardiomyopathies in children," Progress in Pediatric Cardiology, Vol. 25, pages 23-25 (2008)	☐
	48	Yoshida, "Well-illustrated Diagnostics and Treatment of Heart Failure," Professor of Kawasaki Medical University, cardiovascular internal medicine, Circulation, Up-to-Date Vol. 2, No. 4, pages 23-28 (2007)	☐

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	13683236
	Filing Date	2012-11-21
	First Named Inventor	Baldassarre
	Art Unit	
	Examiner Name	
	Attorney Docket Number	26047-0003006

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)	2012-12-05
Name/Print	Janis K. Fraser	Registration Number	34819

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

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

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.

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Electronic Acknowledgement Receipt	
EFS ID:	14388417
Application Number:	13683236
International Application Number:	
Confirmation Number:	5655
Title of Invention:	METHODS OF DISTRIBUTING A PHARMACEUTICAL PRODUCT COMPRISING NITRIC OXIDE GAS FOR INHALATION
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:	26047-0003006
Receipt Date:	05-DEC-2012
Filing Date:	21-NOV-2012
Time Stamp:	13:37:01
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	IDSFOURTH0003006.pdf	62907 f9e3085323fb71f1cd9d95daf4625daf418c492a	no	1

Warnings:
Information:

2	Information Disclosure Statement (IDS) Form (SB08)	SB08FOURTH0003006.pdf	616271 dfcbb9f6add14c0c6e277918ba65381054d39dd1	no	8

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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	: James S. Baldassarre et al.	Art Unit	: Unknown
Serial No.	: 13/683,236	Examiner	: Unknown
Filed	: November 21, 2012	Conf. No.	: 5655
Title	: METHODS OF DISTRIBUTING A PHARMACEUTICAL PRODUCT COMPRISING NITRIC OXIDE GAS FOR INHALATION		

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 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 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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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	13683236
	Filing Date	2012-11-21
	First Named Inventor	Baldassarre
	Art Unit	
	Examiner Name	
	Attorney Docket Number	26047-0003006

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	13683236
	Filing Date	2012-11-21
	First Named Inventor	Baldassarre
	Art Unit	
	Examiner Name	
	Attorney Docket Number	26047-0003006

	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 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.

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	13683236
	Filing Date	2012-11-21
	First Named Inventor	Baldassarre
	Art Unit	
	Examiner Name	
	Attorney Docket Number	26047-0003006

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)	2012-12-06
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.**

Privacy Act Statement

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Electronic Acknowledgement Receipt	
EFS ID:	14400025
Application Number:	13683236
International Application Number:	
Confirmation Number:	5655
Title of Invention:	METHODS OF DISTRIBUTING A PHARMACEUTICAL PRODUCT COMPRISING NITRIC OXIDE GAS FOR INHALATION
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:	26047-0003006
Receipt Date:	06-DEC-2012
Filing Date:	21-NOV-2012
Time Stamp:	13:43:46
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	IDSFIFTH0003006.pdf	62901 10183836c7ce9c4b56cfe8330a2370739bc2e741	no	1

Warnings:
Information:

2	Information Disclosure Statement (IDS) Form (SB08)	SB08Numberfifth260470003006.pdf	528461 e656b355e24b188c054880a844294dcd12359584	no	4

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Total Files Size (in bytes):	591362

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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
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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	: Unknown
Serial No.	: 13/683,236	Examiner	: Unknown
Filed	: November 21, 2012	Conf. No.	: 5655
Title	: METHODS OF DISTRIBUTING A PHARMACEUTICAL PRODUCT COMPRISING NITRIC OXIDE GAS FOR INHALATION		

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Commissioner for Patents
P.O. Box 1450
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
Facsimile: (877) 769-7945

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PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number: 13/683,236

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))	4 minus 3 =	* 1				x 250 =	250
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	2130

APPLICATION AS AMENDED - PART II

		(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($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE($)
AMENDMENT A	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	

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE($)	ADDITIONAL FEE($)	OR	RATE($)	ADDITIONAL FEE($)
AMENDMENT B	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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United States Patent and Trademark Office
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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
13/683,236	11/21/2012	3771	2430	26047-0003006	30	4

CONFIRMATION NO. 5655

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

FILING RECEIPT

OC00000005795419O

Date Mailed: 12/07/2012

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 DIV of 12/820,866 06/22/2010
which is a CON of 12/494,598 06/30/2009 ABN
This application 13/683,236
is a DIV 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: 12/04/2012
The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 13/683,236**

Projected Publication Date: 03/21/2013

Non-Publication Request: No

Early Publication Request: No

Title

METHODS OF DISTRIBUTING A PHARMACEUTICAL PRODUCT COMPRISING NITRIC OXIDE GAS FOR INHALATION

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).

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Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
13/683,236	11/21/2012	James S. Baldassarre	26047-0003006

CONFIRMATION NO. 5655

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

POA ACCEPTANCE LETTER

OC000000057954265

Date Mailed: 12/07/2012

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.

/dgela/

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

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	13683236
	Filing Date	2012-11-21
	First Named Inventor	Baldassarre
	Art Unit	
	Examiner Name	
	Attorney Docket Number	26047-0003006

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	13683236
	Filing Date	2012-11-21
	First Named Inventor	Baldassarre
	Art Unit	
	Examiner Name	
	Attorney Docket Number	26047-0003006

	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)	☐

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
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	Attorney Docket Number	26047-0003006

	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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	First Named Inventor	Baldassarre
	Art Unit	
	Examiner Name	
	Attorney Docket Number	26047-0003006

	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)	☐

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
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	Filing Date	2012-11-21
	First Named Inventor	Baldassarre
	Art Unit	
	Examiner Name	
	Attorney Docket Number	26047-0003006

	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)		
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	First Named Inventor	Baldassarre
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	Attorney Docket Number	26047-0003006

	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	13683236
	Filing Date	2012-11-21
	First Named Inventor	Baldassarre
	Art Unit	
	Examiner Name	
	Attorney Docket Number	26047-0003006

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.**

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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 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:	14410346
Application Number:	13683236
International Application Number:	
Confirmation Number:	5655
Title of Invention:	METHODS OF DISTRIBUTING A PHARMACEUTICAL PRODUCT COMPRISING NITRIC OXIDE GAS FOR INHALATION
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:	26047-0003006
Receipt Date:	07-DEC-2012
Filing Date:	21-NOV-2012
Time Stamp:	12:38:57
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	IDSSIXTH0003006.pdf	62859 fa853dcea6de41bce03414dc601c9cff31ac05a5	no	1

Warnings:
Information:

2	Information Disclosure Statement (IDS) Form (SB08)	SB08Six0003006.pdf	613505 f1d59650f7e6129e5077777c52329c3d88f099de	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):	676364

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.	: 13/683,236	Examiner	: Unknown
Filed	: November 21, 2012	Conf. No.	: 5655
Title	: METHODS OF DISTRIBUTING A PHARMACEUTICAL PRODUCT COMPRISING NITRIC OXIDE GAS FOR INHALATION		

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

22948002.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

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	13683236
	Filing Date	2012-11-21
	First Named Inventor	Baldassarre
	Art Unit	
	Examiner Name	
	Attorney Docket Number	26047-0003006

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

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

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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	13683236
	Filing Date	2012-11-21
	First Named Inventor	Baldassarre
	Art Unit	
	Examiner Name	
	Attorney Docket Number	26047-0003006

	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	13683236
	Filing Date	2012-11-21
	First Named Inventor	Baldassarre
	Art Unit	
	Examiner Name	
	Attorney Docket Number	26047-0003006

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)	2012-12-10
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.**

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:	14423256
Application Number:	13683236
International Application Number:	
Confirmation Number:	5655
Title of Invention:	METHODS OF DISTRIBUTING A PHARMACEUTICAL PRODUCT COMPRISING NITRIC OXIDE GAS FOR INHALATION
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:	26047-0003006
Receipt Date:	10-DEC-2012
Filing Date:	21-NOV-2012
Time Stamp:	13:42:41
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	IDSSEVENTH0003006.pdf	64065 c5f9f9263b36f6bc11fe096a36d31bc83f2a1981	no	2

Warnings:
Information:

2	Information Disclosure Statement (IDS) Form (SB08)	SB08Numberseven260470003006.pdf	612433 5e2b9192021c4463a2f2cd693f96dcb0540edb36	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):	744410		

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.	: 13/683,236	Examiner	: Unknown
Filed	: November 21, 2012	Conf. No.	: 5655
Title	: METHODS OF DISTRIBUTING A PHARMACEUTICAL PRODUCT COMPRISING NITRIC OXIDE GAS FOR INHALATION		

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)
13/683,417 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

228948004.doc

UNITED STATES PATENT AND TRADEMARK OFFICE

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

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DEC 17 2012
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Doc Code: TRACK1.GRANT

Decision Granting Request for Prioritized Examination (Track I or After RCE)	Application No.: 13/683,236

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 JoAnne Burke at 571-272-4584. In his/her absence, calls may be directed to Brian Brown, 571-272-5338.

/JoAnne Burke/
[*Signature*]

Petitions Examiner
(Title)

U.S. Patent and Trademark Office
PTO-2298 (Rev. 02-2012)

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	13683236
	Filing Date	2012-11-21
	First Named Inventor	Baldassarre
	Art Unit	3771
	Examiner Name	
	Attorney Docket Number	26047-0003006

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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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					
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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							☐
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	13683236
	Filing Date	2012-11-21
	First Named Inventor	Baldassarre
	Art Unit	3771
	Examiner Name	
	Attorney Docket Number	26047-0003006

	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	13683236
	Filing Date	2012-11-21
	First Named Inventor	Baldassarre
	Art Unit	3771
	Examiner Name	
	Attorney Docket Number	26047-0003006

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

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Electronic Acknowledgement Receipt	
EFS ID:	14567329
Application Number:	13683236
International Application Number:	
Confirmation Number:	5655
Title of Invention:	METHODS OF DISTRIBUTING A PHARMACEUTICAL PRODUCT COMPRISING NITRIC OXIDE GAS FOR INHALATION
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:	26047-0003006
Receipt Date:	27-DEC-2012
Filing Date:	21-NOV-2012
Time Stamp:	13:47:05
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_0003006eighthIDS.pdf	612176 b9e9e3a8fc3861de3b4ce8f80f4606ec06b709dd	no	4

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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.

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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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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/683,236	11/21/2012	James S. Baldassarre	26047-0003006	5655

94169 7590 01/03/2013

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

EXAMINER	
ARNOLD, ERNST V	
ART UNIT	PAPER NUMBER
1613	
MAIL DATE	DELIVERY MODE
01/03/2013	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)	
	13/683,236	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.

Information Disclosure Statement

All information disclosure statements have been considered by the Examiner.

Specification

The abstract of the disclosure is objected to because the single sentence abstract is not descriptive of the claimed subject matter and merely repeats what is in the title. The abstract should describe the disclosure sufficiently to assist readers in deciding whether there is a need for consulting the full patent text for details. The language should be clear and concise and *should not repeat information given in the title*. Currently, the Abstract is:

> Disclosed are methods of distributing a pharmaceutical product comprising nitric oxide gas for inhalation.

And the title is:

> METHODS OF DISTRIBUTING A PHARMACEUTICAL PRODUCT COMPRISING NITRIC OXIDE GAS FOR INHALATION

Correction is required. See MPEP § 608.01(b).

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1-30 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. The independent claims are directed to mental processes which are non-statutory subject matter. In claims 1, 11, 21 and 27, for example, the step of "providing a source of nitric oxide gas" encompasses providing a catalog or website and it is not necessarily an active step. Even if the claim were to be interpreted as providing the NO gas itself, there is still no step of actually administering the gas, and the entire claim could result in nothing more than warning a medical provider NOT to administer gas. The Examiner cannot see how a method of: "Here, take this nitric oxide gas source, but do not do anything with it" is patent eligible. Furthermore, the step of providing a source of nitric oxide gas (or the gas itself) is extra-solution activity, not explicitly linked (or necessary) for the performance of the "critical" steps of determining when a warning should be generated. The steps of providing first and second warnings encompass providing a label or are thought processes and are not necessarily active steps. Therefore, the independent claims do not meet the requirements of 35 USC 101. The dependent claims that may recite an active step such as "perform at least one diagnostic process" are also rejected under 35 USC 101 because MPEP 2106 states: " A claim that covers both statutory and non-statutory embodiments (under the broadest reasonable interpretation of the claim when read in light of the specification and in view of one skilled in the art) embraces subject matter

that is not eligible for patent protection and therefore is directed to non-statutory subject matter. Such claims fail the first step and should be rejected under **35 U.S.C. 101** , for at least this reason."

Please note that the Examiner has consulted with the Technology Centers resident expert Quality Assurance Specialist on 35 USC 101 to assist in the claim analysis and drafting of this rejection.

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

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	13683236
	Filing Date	2012-11-21
	First Named Inventor	Baldassarre
	Art Unit	
	Examiner Name	
	Attorney Docket Number	26047-0003006

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Receipt date: 12/03/2012	Application Number	13683236 13683236 - GAU: 1613
INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99**)	Filing Date	2012-11-21
	First Named Inventor	Baldassarre
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	Examiner Name	
	Attorney Docket Number	26047-0003006

	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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	Attorney Docket Number	26047-0003006

	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	26047-0003006

	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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	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	12/31/2012

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	First Named Inventor	Baldassarre	
	Art Unit		
	Examiner Name		
	Attorney Docket Number	26047-0003006	

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)	2012-12-03
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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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	13683236
	Filing Date	2012-11-21
	First Named Inventor	Baldassarre
	Art Unit	
	Examiner Name	
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Receipt date: 12/04/2012	Application Number	13683236 13683236 - GAU: 1613
INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99**)	Filing Date	2012-11-21
	First Named Inventor	Baldassarre
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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)	☐
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	6	Kulik, "Inhaled nitric oxide in the management of congenital heart disease," Current Opinion in Cardiology, Vol. 11, pages 75-80 (1996)	☐
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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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	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	☐
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	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)	☐
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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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	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	☐
	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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	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	☐
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	4	Pepke-Zaba et al., "Inhaled nitric oxide as a cause of selective pulmonary vasodilation in pulmonary hypertension," The Lancet, Vol. 338, pages 1173-1174 (1991)	☐
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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	26047-0003006

	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	☐
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	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)	☐
	16	Shapiro et al., "Diagnostic Dilemmas: Diastolic Heart Failure Causing Pulmonary Hypertension and Pulmonary Hypertension Causing Diastolic Dysfunction," Advances in Pulmonary Hypertension, Vol. 5(1), pages 13-20 (2006) http://www.phaonlineuniv.org/sites/default/files/spr_2006.pdf	☐
	17	"Sibutramine-metformin Combination vs. Sibutramine and Metformin Monotherapy in Obese Patients, page 3, ClinicalTrials.gov, <<http://clinicaltrials.gov/ct2/showNCT00941382>> Sponsored by Laboratorios Silanes S.A. de C.V. and Jorge González Canudas, July 15, 2009	☐
	18	Singh et al., "Nitric Oxide, the biological mediator of the decade: fact of fiction?," Eur. Respir. J. , Vol. 10, pages 699-707 (1997)	☐
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	28	The American Illustrated Medical Dictionary (Dorland, 7th ed., page 113) (1914)	☐
	29	The Effects of Nitric Oxide for Inhalation on the Development of Chronic Lung Disease in Pre-Term Infants, from ClinicalTrials.gov archive, NCT00551642, 10/30/2007, 3 pages	☐
	30	"The Encarta Webster's Dictionary of the English Language (2004) is the second edition of the Encarta World Dictionary, published 1999, <<http://encarta.msn.com/encnet/features/dictionary/dictionaryhome.aspx>>; used to look up the definitions of "precaution" and "exclusion"	☐
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	39	UTMB Respiratory Care Services, "Delivery of Inhaled Nitric Oxide Therapy through an Adult or Pediatric Nasal Cannula," 4 pages, (2003)	☐
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	42	Weinberger et al., "The Toxicology of Inhaled Nitric Oxide," Toxicological Sciences, Vol. 59, pages 5-16 (2001)	☐
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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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	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	☐
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Name/Print	Janis K. Fraser	Registration Number	34819

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Inventor Information for 13/683236

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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	Attorney Docket Number	26047-0003006	

/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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Receipt date: 12/10/2012	Application Number	13683236	13683236 - 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	26047-0003006	

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Signature	/Janis K. Fraser/	Date (YYYY-MM-DD)	2012-12-10
Name/Print	Janis K. Fraser	Registration Number	34819

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	Application Number	13683236
	Filing Date	2012-11-21
	First Named Inventor	Baldassarre
	Art Unit	3771
	Examiner Name	
	Attorney Docket Number	26047-0003006

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	Attorney Docket Number	26047-0003006	

/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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	13683236	BALDASSARRE ET AL.
	Examiner	Art Unit
	ERNST ARNOLD	1613

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Search Notes	Date	Examiner
consultation with QAS Majorie Moran on 101 issues and drafting of rejection	12/21/12	eva

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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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	First Named Inventor	Baldassarre	
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	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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	1	EP1682672	EP		2006-07-26			☐
	2	WO2005004884	WO		2005-01-20			☐
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	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)	☐
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	9	Azeka et al., "Effects of Low Doses of Inhaled Nitric Oxide Combined with Oxygen for the Evaluation of Pulmonary Vascular Reactivity in Patients with Pulmonary Hypertension," Pedatric Cardiol., Vol. 23, pages 20-26 (2002)	☐
	10	Barrington et al., "Inhaled Nitric Oxide for Preterm Infants: A Systematic Review," Pediatrics, Vol. 120; pages 1088-1099, DOI: 10.1542/peds (2007)	☐
	11	Barst et al., "Nitric Oxide in Combination with Oxygen versus Either Oxygen Alone or Nitric Oxide Alone for Acute Vasodilator Testing in Children with Pulmonary Hypertension: A Multicenter, Randomized Study," INO Therapeutics/ Ikaria, Baltimore Convention Center, May 3, 2009, 2 pages, Abstract, downloaded 7/2/2009 from http://127.0.0.1:9080/ PAS09A1/view.y?nu=PAS09L1_1507	☐

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	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)	☐
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	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)	☐
	19	Bin-Nun et al., "Role of iNO in the modulation of pulmonary vascular resistance," Journal of Perinatology, Vol. 28, pages S84-S92 (2008)	☐
	20	Bland, "Pulmonary vascular dysfuction in preterm lambs with chronic lung disease," Am J Physical Lung Cell Mol. Physiol., Vol. 285: L76-L85 (2003)	☐
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	22	Bocchi et al.,"Inhaled Nitric Oxide Leading to Pulmonary Edema in Stable Severe Heart Failure," The American Journal of Cardiology, Vol. 74, pages 70-72 (1994)	☐

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	23	Bolooki, Clinical Application of the Intra-Aortic Balloon Pump, 3rd Ed., pages 252-253 (1998)	☐
	24	Branson, "Inhaled Nitric Oxide in Adults," The Science Journal of the American Association for Respiratory Care 1997 Open Forum Abstracts, December 7, 1997, 2 pages, retrieved at <<http://www.rcjournal.com/abstracts/1997/?id=A00000929>> on 12/22/2010	☐
	25	Braunwald, Heart Failure, chapter 233 of Harrison's Principles of Internal Medicine, 14th Edition, pages1287-1291 and 1360 (1998)	☐
	26	Bublik et al., "Pediatric cardiomyopathy as a chronic disease: A perspective on comprehensive care programs, Progress in Pediatric," Pediatric Cardiology, Vol. 25, pages 103-111 (2008)	☐
	27	Budts et al., "Residual pulmonary vasoreactivity to inhaled nitric oxide in patients with severe obstructive pulmonary hypertension and Eisenmenger syndrome," Heart, Vol. 86, pages 553-558 (2001)	☐
	28	Canadian Office Action mailed May 31, 2011 for Canadian Patent Application No. 2671029, a counterpart foreign application of US application no. 12/494,598	☐
	29	Clark et al., "Low-Dose Nitric Oxide Therapy for Persistent Pulmonary Hypertension: 1-Year Follow-up," Journal of Perinatology, Vol. 23, pages 300-303 (2003)	☐
	30	Clark et al., "Low-Dose Nitric Oxide Therapy for Persistent Pulmonary Hypertension of the Newborn," New England Journal of Medicine, Vol. 342, No. 7, pages 469-474 (2000)	☐
	31	Cockrill et al., "Comparison of the Effects of Nitric Oxide, Nitroprusside, and Nifedipine on Hemodynamics and Right Ventricular Contractibility in Patients With Chronic Pulmonary Hypertension," CHEST, Vol. 119, No. 1, pages 128-136 (2001)	☐
	32	Comparison of Supplemental Oxygen and Nitric Oxide for Inhalation in the Evaluation of the Reactivity of the Pulmonary Vasculature During Acute Pulmonary Vasodilator Testing, http://clinicaltrials.gov/archive/NCT00626028/2009_01_12 January 12, 2009	☐
	33	Cornfield et al., "Randomized, Controlled Trial of Low-dose Inhaled Nitric Oxide in the Treatment of Term and Near-term Infants With Respiratory Failure and Pulmonary Hypertension," Pediatrics, Vol. 104, No. 5, pages 1089-1094 (1999)	☐

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	34	Cox et al., "Factors Associated with Establishing a Causal Diagnosis for Children with Cardiomyopathy," Pediatrics, Vol. 118, No 4, pages 1519-1531 (2006)	☐
	35	Cujec 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(9), pages 816-824 (1997)	☐
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	37	Davidson et al., "Inhaled nitric oxide for the early treatment of persistent pulmonary hypertension of the term newborn: a randomized, double-masked, placebo-controlled, dose-response, multicenter study," PEDIATRICS, Vol. 101 (3 Pt 1), pages 325-34 (1998)	☐
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	49		☐
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☒ 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)	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.
13/683,236	11/21/2012	424	1613	26047-0003006

APPLICANTS

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

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

This application is a DIV of 12/820,866 06/22/2010 ABN
which is a CON of 12/494,598 06/30/2009 ABN
This application 13/683,236 11/21/2012
is a DIV of 13/651,660 10/15/2012
which is a CON of 12/821,041 06/22/2010 PAT 8,293,284
which is a CON of 12/494,598 06/30/2009 ABN

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

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12/04/2012

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		30	4

ADDRESS

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

TITLE

METHODS OF DISTRIBUTING A PHARMACEUTICAL PRODUCT COMPRISING NITRIC OXIDE GAS FOR INHALATION

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	Application Number	13683236
	Filing Date	2012-11-21
	First Named Inventor	Baldassarre
	Art Unit	
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Receipt date: 12/07/2012	Application Number	13683236 13683236 - GAU: 1613
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	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)	☐
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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)	☐
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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)	☐
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	48	Fish & Richardson, Brief on Appeal in U.S. Serial No. 12/820,866, filed October 4, 2011 (211 pages)	☐
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Name/Print	Janis K. Fraser	Registration Number	34819

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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
13/683,236	11/21/2012	James S. Baldassarre	26047-0003006

CONFIRMATION NO. 5655

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

PUBLICATION NOTICE

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Title:METHODS OF DISTRIBUTING A PHARMACEUTICAL PRODUCT COMPRISING NITRIC OXIDE GAS FOR INHALATION

Publication No.US-2013-0068223-A1
Publication Date:03/21/2013

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.

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	: James S. Baldassarre et al.	Art Unit	: 1613
Serial No.	: 13/683,236	Examiner	: Ernst V. Arnold
Filed	: November 21, 2012	Conf. No.	: 5655
Title	: METHODS OF DISTRIBUTING A PHARMACEUTICAL PRODUCT COMPRISING NITRIC OXIDE GAS FOR INHALATION		

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

AMENDMENT IN REPLY TO ACTION OF JANUARY 3, 2013

The above-identified application has been granted prioritized examination under Track 1. This Reply is being filed within three months of the Office action's mailing date.

Please amend the application as follows:

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 2, 2013
Date of Deposit or Transmission

/Nancy Bechet/
Signature

Nancy Bechet
Typed or Printed Name of Person Signing Certificate

Amendment to the Abstract:

Replace the abstract at page 30 with the following amended abstract:

Disclosed are methods of distributing a pharmaceutical product comprising nitric oxide gas ~~for inhalation~~. The methods include supplying a source of nitric oxide gas to a medical provider, informing the medical provider about a recommended dose of inhaled nitric oxide gas for treatment of neonates with hypoxic respiratory failure, and providing a warning about use of inhaled nitric oxide in patients with pre-existing left ventricular dysfunction.

Amendments to the Claims:

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

Listing of Claims:

1. (Currently amended) A method of distributing a pharmaceutical product, the method comprising:

~~providing~~supplying a source of nitric oxide gas to a medical provider responsible for treating a plurality of neonates with hypoxic respiratory failure, including some who do not have left ventricular dysfunction and who are not dependent on right-to-left shunting of blood, wherein the source comprises a cylinder of compressed gas and/or a delivery device suitable to deliver nitric oxide gas for inhalation by a patient;

informing the medical provider that a recommended dose of inhaled nitric oxide gas for treatment of neonates with hypoxic respiratory failure is 20 ppm nitric oxide;

providing a first warning to the medical provider that inhaled nitric oxide is contraindicated in the treatment of neonates dependent on right-to-left shunting of blood; and

providing a second warning to the medical provider, distinct from the first warning, that in patients with pre-existing left ventricular dysfunction, inhaled nitric oxide may increase pulmonary capillary wedge pressure (PCWP), leading to pulmonary edema, the second warning being sufficient to cause a medical provider considering inhaled nitric oxide treatment for a plurality of neonatal patients who (a) are suffering from a condition for which inhaled nitric oxide is indicated, and (b) have pre-existing left ventricular dysfunction, to elect to avoid treating one or more of the plurality of patients with inhaled nitric oxide in order to avoid putting the one or more patients at risk of pulmonary edema.

2. (Currently amended) The method of claim 1, further comprising generating the source of nitric oxide gas prior to ~~providing~~supplying the source to the medical provider.

3. (Canceled)

4. (Currently amended) The method of claim 1, further comprising generating the source of nitric oxide gas by a method comprising compressing nitric oxide and nitrogen gases under high pressure, prior to ~~providing~~supplying the source to the medical provider.

5. (Canceled)

6. (Currently amended) The method of claim 1, wherein the dose recommendation and the first and second warnings appear in prescribing information supplied to the medical provider with the source of nitric oxide gas.

7. (Currently amended) The method of claim 1, ~~wherein, following provision of the source of nitric oxide gas and the first and second warnings to the medical provider, the medical provider~~further comprising:

~~performs~~performing at least one diagnostic process to identify a first neonate patient who has hypoxic respiratory failure and is a candidate for 20 ppm inhaled nitric oxide treatment, wherein the first neonate patient is not dependent on right to left shunting of blood;

~~determines~~determining that the first neonate patient has left ventricular dysfunction; ~~and~~

~~evaluates~~evaluating the potential benefit of treating the first neonate patient with 20 ppm inhaled nitric oxide vs. the potential risk described in the second warning that inhaled nitric oxide could cause an increase in PCWP leading to pulmonary edema in patients who have left ventricular dysfunction, in order to arrive at a decision of whether or not to treat the first neonate patient with inhaled nitric oxide;

identifying a second neonatal patient as having hypoxic respiratory failure, not being dependent on right to left shunting of blood, and not having left ventricular dysfunction; and

treating the second neonatal patient with 20 ppm inhaled nitric oxide.

8. (Currently amended) The method of claim 1, ~~wherein, following provision of the source of nitric oxide gas and the first and second warnings to the medical provider, the medical provider~~further comprising:

~~performs~~performing at least one diagnostic process to identify a plurality of neonate patients who have hypoxic respiratory failure and are candidates for inhaled nitric oxide treatment, wherein the patients of the plurality are not dependent on right to left shunting of blood;

~~determines~~determining prior to treatment with inhaled nitric oxide whether or not each patient of the plurality has left ventricular dysfunction; ~~and~~

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

treating the first patient with 20 ppm inhaled nitric oxide;

determining that other patients of the plurality do have left ventricular dysfunction; and

for each patient of the plurality determined to have left ventricular dysfunction, ~~evaluates~~evaluating on a case-by-case basis the potential benefit of treating the patient with 20 ppm inhaled nitric oxide vs. the potential risk described in the second warning that inhaled nitric oxide could cause an increase in PCWP, leading to pulmonary edema;

for at least one patient of the plurality determined to have left ventricular dysfunction, determining that the potential benefit of the treatment outweighs the potential risk described in the second warning; and

treating the at least one patient with 20 ppm inhaled nitric oxide.

9. (Currently amended) The method of claim 7, wherein the dose recommendation and the first and second warnings appear in prescribing information supplied to the medical provider with the source of nitric oxide gas.

10. (Currently amended) The method of claim 8, wherein the dose recommendation and the first and second warnings appear in prescribing information supplied to the medical provider with the source of nitric oxide gas.

11. (Currently amended) A method of distributing a pharmaceutical product, the method comprising:

~~providing~~supplying a source of nitric oxide gas to a medical provider responsible for treating a plurality of neonates with hypoxic respiratory failure, including some who do not have left ventricular dysfunction and who are not dependent on right-to-left shunting of blood, wherein the source comprises a cylinder of compressed gas and/or a delivery device suitable to deliver nitric oxide gas for inhalation by a patient, wherein the source comprises a cylinder of compressed gas and/or a delivery device suitable to deliver nitric oxide gas for inhalation by a patient;

informing the medical provider that a recommended dose of inhaled nitric oxide gas for treatment of neonates with hypoxic respiratory failure is 20 ppm nitric oxide;

providing a first warning to the medical provider that inhaled nitric oxide is contraindicated in the treatment of neonates dependent on right-to-left shunting of blood; and

providing a second warning to the medical provider, distinct from the first warning, that in patients with pre-existing left ventricular dysfunction, inhaled nitric oxide may increase PCWP leading to pulmonary edema, the second warning being sufficient to cause a medical provider considering inhaled nitric oxide treatment for a plurality of neonatal patients who (a) are suffering from a condition for which inhaled nitric oxide is indicated, and (b) have pre-existing left ventricular dysfunction, to evaluate (i) the potential benefit of treating the neonatal patients with 20 ppm inhaled nitric oxide vs. (ii) the potential risk that the 20 ppm inhaled nitric oxide could cause pulmonary edema in the neonatal patients due to the neonatal patients' left ventricular dysfunction, and accordingly elect to avoid treating one or more of the neonatal patients with inhaled nitric oxide in order to avoid putting the one or more neonatal patients at risk of pulmonary edema.

12. (Currently amended) The method of claim 11, further comprising generating the source of nitric oxide gas[[,]] prior to ~~providing~~supplying the source to the medical provider.

13. (Currently amended) The method of claim 12, wherein the source of nitric oxide gas is a delivery device that delivers a gaseous ~~blend of~~ mixture comprising nitric oxide and nitrogen for inhalation by a patient.

14. (Currently amended) The method of claim 11, further comprising generating the source of nitric oxide gas by a method comprising compressing nitric oxide and nitrogen gases under high pressure, prior to ~~providing~~supplying the source to the medical provider.

15. (Currently amended) The method of claim 11, wherein the source of nitric oxide gas ~~is~~ comprises a cylinder containing a gaseous blend of nitric oxide and nitrogen ~~provided~~supplied to the medical provider as a compressed gas ~~in a cylinder~~ under high pressure.

16. (Currently amended) The method of claim 11, wherein the dose recommendation and the first and second warnings appear in prescribing information supplied to the medical provider with the source of nitric oxide gas.

17. (Currently amended) The method of claim 11, ~~wherein, following provision of the source of nitric oxide gas and the first and second warnings to the medical provider, the medical provider~~further comprising:

~~performs~~performing at least one diagnostic process to identify a first neonatal patient who has hypoxic respiratory failure and is a candidate for inhaled nitric oxide treatment, wherein the first neonatal patient is not dependent on right to left shunting of blood;

~~determines~~determining prior to treatment with inhaled nitric oxide that the first neonatal patient has left ventricular dysfunction; ~~and~~

~~evaluating~~evaluating the potential benefit of treating the first neonatal patient with 20 ppm inhaled nitric oxide vs. the potential risk described in the second warning that inhaled nitric oxide could cause an increase in PCWP leading to pulmonary edema in patients who have left ventricular dysfunction, in order to arrive at a decision of whether or not to treat the first neonatal patient with inhaled nitric oxide;

identifying a second neonatal patient as having hypoxic respiratory failure, not being dependent on right to left shunting of blood, and not having left ventricular dysfunction; and

treating the second neonatal patient with 20 ppm inhaled nitric oxide.

18. (Currently amended) The method of claim 11, ~~wherein, following provision of the source of nitric oxide gas and the first and second warnings to the medical provider, the medical provider~~further comprising:

~~performs~~performing at least one diagnostic process to identify a plurality of neonatal patients who have hypoxic respiratory failure and are candidates for inhaled nitric oxide treatment, wherein the patients of the plurality are not dependent on right to left shunting of blood;

~~determines~~determining prior to treatment with inhaled nitric oxide whether or not each patient of the plurality has left ventricular dysfunction; and

for each patient of the plurality determined to have left ventricular dysfunction, ~~evaluates~~evaluating on a case-by-case basis the potential benefit of treating the patient with 20 ppm inhaled nitric oxide vs. the potential risk described in the second warning that inhaled nitric oxide could cause an increase in PCWP leading to pulmonary edema;

for at least one patient of the plurality determined to have left ventricular dysfunction, determining that the potential benefit of the treatment outweighs the potential risk described in the second warning; and

treating the at least one patient with 20 ppm inhaled nitric oxide.

19. (Currently amended) The method of claim 17, wherein the dose recommendation and the first and second warnings appear in prescribing information supplied to the medical provider with the source of nitric oxide gas.

20. (Currently amended) The method of claim 18, wherein the dose recommendation and the first and second warnings appear in prescribing information supplied to the medical provider with the source of nitric oxide gas.

21. (Currently amended) A method of distributing a pharmaceutical product, the method comprising:

~~providing~~supplying a source of nitric oxide gas to a medical provider responsible for treating a plurality of neonates with hypoxic respiratory failure, including some who do not have left ventricular dysfunction and who are not dependent on right-to-left shunting of blood, wherein the source comprises a cylinder of compressed gas and/or a delivery device suitable to deliver nitric oxide gas for inhalation by a patient;

informing the medical provider that a recommended dose of inhaled nitric oxide gas for treatment of neonates with hypoxic respiratory failure is 20 ppm nitric oxide;

providing a first warning to the medical provider that inhaled nitric oxide is contraindicated in the treatment of neonates dependent on right-to-left shunting of blood;

providing a second warning to the medical provider, distinct from the first warning, stating that patients who have pre-existing left ventricular dysfunction and are treated with inhaled nitric oxide may experience pulmonary edema, and recommending that, if pulmonary edema occurs in a patient who has pre-existing left ventricular dysfunction and is treated with inhaled nitric oxide, the treatment with inhaled nitric oxide should be discontinued.

22. (Currently amended) The method of claim 21, further comprising generating the source of nitric oxide gas prior to ~~providing it~~supplying the source to the medical provider.

23. (Currently amended) The method of claim 22, wherein the source of nitric oxide ~~is a compressed gas that is a~~ gas comprises a cylinder containing a gaseous blend of nitric oxide and nitrogen supplied to the medical provider as a compressed gas under high pressure.

24. (Currently amended) The method of claim 21, further comprising generating the source of nitric oxide gas by a method comprising compressing nitric oxide and nitrogen gases under high pressure, prior to ~~providing~~supplying the source to the medical provider.

25. (Currently amended) The method of claim 21, wherein the dose recommendation and the first and second warnings appear in prescribing information supplied to the medical provider with the source of nitric oxide gas.

26. (Currently amended) The method of claim 21, ~~wherein, following provision of the source of nitric oxide gas and the first and second warnings to the medical provider, the medical provider~~further comprising:

~~performs~~performing at least one diagnostic process to identify a neonatal patient who is a candidate for inhaled nitric oxide treatment;

~~determines~~determining prior to treatment with inhaled nitric oxide that the neonatal patient is not dependent on right to left shunting of blood, but does have left ventricular dysfunction consistent with a pulmonary capillary wedge pressure greater than or equal to 20 mm Hg;

~~treats~~treating the neonatal patient with 20 ppm inhaled nitric oxide, whereupon the patient experiences pulmonary edema; and

~~follows~~following the recommendation in the second warning ~~to discontinue,~~ discontinuing the treatment with inhaled nitric oxide due to the patient's pulmonary edema.

27. (Currently amended) A method of distributing a pharmaceutical product, the method comprising:

~~providing~~supplying a source of nitric oxide gas to a medical provider responsible for treating a plurality of neonates with hypoxic respiratory failure, including some who do not have left ventricular dysfunction and who are not dependent on right-to-left shunting of blood, wherein the source comprises a cylinder of compressed gas and/or a delivery device suitable to deliver nitric oxide gas for inhalation by a patient;

informing the medical provider that a recommended dose of inhaled nitric oxide gas for treatment of neonates is 20 ppm nitric oxide;

providing a first warning to the medical provider that inhaled nitric oxide is contraindicated in the treatment of neonates dependent on right-to-left shunting of blood;

providing a second warning to the medical provider, distinct from the first warning, stating that patients who have pre-existing left ventricular dysfunction and are treated with inhaled nitric oxide may experience hypotension, and recommending that, if hypotension occurs in a patient who has pre-existing left ventricular dysfunction and is treated with inhaled nitric oxide, the treatment with inhaled nitric oxide should be discontinued.

28. (Currently amended) The method of claim 27, further comprising generating the source of nitric oxide gas prior to ~~providing~~supplying the source to the medical provider.

29. (Currently amended) The method of claim 27, further comprising generating the source of nitric oxide gas by a method comprising compressing nitric oxide and nitrogen gases under high pressure, prior to ~~providing~~supplying the source to the medical provider.

30. (Currently amended) The method of claim 27, ~~wherein, following provision of the source of nitric oxide gas and the first and second warnings to the medical provider, the medical provider~~further comprising:

~~performs~~performing echocardiography to identify a neonate patient who is a candidate for inhaled nitric oxide treatment;

~~determines~~determining prior to treatment with inhaled nitric oxide that the neonate patient is not dependent on right to left shunting of blood, but does have left ventricular dysfunction consistent with a pulmonary capillary wedge pressure greater than or equal to 20 mm Hg;

~~treats~~treating the neonate patient with 20 ppm inhaled nitric oxide, whereupon the patient experiences hypotension; and

~~follows~~following the recommendation in the second warning ~~to discontinue~~, discontinuing the treatment with inhaled nitric oxide due to the patient's hypotension.

31. (New) The method of claim 8, wherein the at least one patient is monitored for evidence of increased PCWP and/or for evidence of pulmonary edema during treatment with 20 ppm inhaled nitric oxide.

32. (New) The method of claim 18, wherein the at least one patient is monitored for evidence of increased PCWP and/or for evidence of pulmonary edema during treatment with 20 ppm inhaled nitric oxide.

REMARKS

Upon entry of the above amendment, claims 1, 2, 4, and 6-32 will be pending and under examination, claims 3 and 5 having been canceled and new claims 31 and 32 added. The total number of independent claims remains at four and the total number of dependent claims remains at 30, so the application still qualifies for Track 1 status.

Independent claims 1, 11, 21, and 27 are amended to specify that a source of nitric oxide gas is "supplied" to a medical provider responsible for treating a plurality of neonates with hypoxic respiratory failure, including some who do not have left ventricular dysfunction and who are not dependent on right-to-left shunting of blood, and that the source of nitric oxide gas comprises a cylinder of compressed gas and/or a delivery device suitable to deliver nitric oxide gas for inhalation by a patient. This amendment is supported in the specification as filed, including at paragraphs [0008] and [0021]. The dependent claims are amended to maintain consistency with the independent claims. In addition, claims 7, 8, 17, and 18 are amended to include a treatment step, a limitation supported throughout the specification, e.g., at [0004], [0008], and [0009]. New claims 31 and 32 are implicitly supported, e.g., at [0004], [0008]-[0010], [0017], [0019], and [0065]. No new matter has been added.

Interview summary

Applicant's undersigned representative spoke with SPE Marjorie Moran by telephone on March 14, 2013, in order to benefit from SPE Moran's expertise in evaluating whether claims meet the patent-eligible subject matter requirement under 35 USC § 101. The outstanding rejection under § 101 and possible amendments to the claims intended to overcome the rejection were discussed. No agreement was reached. Applicant sincerely thanks SPE Moran for the very helpful discussion.

Objection to the specification

The Office action at page 2 objects to the abstract of the disclosure as not being sufficiently descriptive of the claimed subject matter. The abstract has been amended to make it more descriptive. Withdrawal of the objection is respectfully requested.

Rejection of the claims

All of the claims are rejected on a single ground: for lack of statutory subject matter under 35 U.S.C. § 101. Applicant traverses this rejection, but also notes with appreciation the implicit conclusion (implied by the absence of any other rejections in the Office action) that the Office has determined there is no other basis for rejecting the present claims.[1]

A. Independent claims

Applicant will first address the rejection as applied to the independent claims (claims 1, 11, 21, and 27), as presently amended.

The Office action begins at page 3 by stating that the rejection is based on an interpretation of the independent claims as being directed to "mental processes." To justify this conclusion, the Office provides an interpretation of some of the steps of the independent claims, beginning with the first step: **"In claims 1, 11, 21 and 27, for example, the step of 'providing a source of nitric oxide gas' encompasses providing a catalog or website and it is not necessarily an active step.**" Applicants respectfully disagree. Even prior to the present amendments, the independent claims are not directed to "mental processes," i.e., processes that can be accomplished merely by *thinking*. Rather, each independent claim recites a process that includes several active steps that cannot be performed merely by thinking.

For example, even if the step of supplying a source of nitric oxide gas did encompass "providing a catalog or website," as alleged in the Office action, that action would plainly

[1] MPEP 2106.III.: "Under the principles of compact prosecution, each claim should be reviewed for compliance with every statutory requirement for patentability in the initial review of the application, even if one or more claims are found to be deficient with respect to the patent-eligibility requirement of 35 U.S.C. 101. Thus, Office personnel should state all non-cumulative reasons and bases for rejecting claims in the first Office action."

qualify as an "active step," because it could not be accomplished merely by thinking. (If this is not what the Examiner means by "not necessarily an active step," clarification is respectfully requested.) *Providing* a catalog or website to a medical provider cannot be done by purely mental activity, e.g., by thinking about it, but rather requires an active step of information transmission to the recipient medical provider, such as creating the website or printing/mailing the catalog or setting out information in a display. The Office action does not say how something (even a catalog or website) can be "provided" to a medical provider merely by thinking about it. Even under the Examiner's interpretation, a step of providing a source of nitric oxide gas to a medical provider requires actions that are not purely mental.

Nonetheless, in an effort to moot the issue and advance the case to allowance, applicants have amended each of the independent claims to state that the "source of nitric oxide gas … comprises a cylinder of compressed gas and/or a delivery device suitable to deliver nitric oxide gas for inhalation by a patient." Furthermore, the independent claims now recite "supplying" the source, rather than "providing" it. Thus, the first step of each independent claim involves an incontrovertibly active step in which a physical object (a cylinder or device) is supplied to a medical provider. Because the claims are not drawn to "mental processes," the grounds for the rejection have been overcome, and the rejection should be withdrawn.

The Office action states, "**Even if the claim were to be interpreted as providing the NO gas itself, there is still no step of actually administering the gas, and the entire claim could result in nothing more than warning a medical provider NOT to administer gas. The Examiner cannot see how a method of: 'Here, take this nitric oxide gas source, but do not do anything with it' is patent eligible.**" Applicants respectfully disagree.

First, U.S. law does not require that a claim directed to *a method of distributing a product* necessarily include a step of "administering" the product. The Examiner has cited no legal basis for imposing such a requirement in a claim that is not drawn to a method of treatment. The independent claims specify *supplying* the source of nitric oxide to the medical provider, *informing* the medical provider about a very specific recommended dose, and also *providing two different warnings* to the medical provider, warnings that give vital information to the medical

provider that permit the medical provider to make important decisions about whether it is appropriate to treat a given patient presenting with a condition described in the warning. Furthermore, the Office seems to have missed the fact that, even prior to the present amendment, two claims (claims 26 and 30) specified a treatment step. With the above amendment, now each of claims 7, 8, 17, 18, 26, and 30 (and their dependent claims 9, 10, 19, 20, 31, and 32) requires that treatment with inhaled nitric oxide occur.

Second, it is not true that "**the entire claim could result in nothing more than warning a medical provider NOT to administer gas.")** Practice of the invention of the independent claims will always result in more than simply "warning the medical provider NOT to administer gas." The first step results in supply of the source of gas itself. The second step facilitates administration of a recommended dose to treat a particular condition. The third step calls for providing a warning to the medical provider that inhaled nitric oxide is contraindicated in the treatment of neonates dependent on right-to-left shunting of blood. The fourth step calls for providing a second warning: in claim 1 this second warning is that, in patients with pre-existing left ventricular dysfunction (LVD), inhaled nitric oxide may increase pulmonary capillary wedge pressure leading to pulmonary edema. None of the four steps, whether taken separately or together, can be fairly summarized as "nothing more than warning a medical provider not to administer gas." The Examiner's assertion to the contrary ignores the actual language of these claims. It also ignores the fact that some of the dependent claims *require* treatment with the gas.

Third, implicit in the above-quoted passage from the Office action is the erroneous assertion that the third and fourth warning steps convert the claimed method into mere instruction to "not do anything." There is no basis in the claim language for such an interpretation. To practice the invention as claimed, one cannot simply say "Here, take this nitric oxide gas source, but do not do anything with it." Rather, one must perform the active step of "supplying" the nitric oxide source to a medical provider as set forth in the claims, and also the active step of "informing" the medical provider of the recommended dose for treatment of neonates with hypoxic respiratory failure. Further, the additional acts of "providing" the first and second warnings are required. It is true that practice of the third and fourth warning steps of

the independent claims will cause medical providers not to administer nitric oxide gas to certain patients, *e.g.*, certain patients having the conditions associated with the warnings. However, providing the first and second warnings does not interfere with or in any way discourage the use of the supplied gas source by a medical provider to treat, for example, neonate patients with hypoxic respiratory failure who do not have the conditions addressed in the first and second warnings. In fact, practice of all the active steps of the independent claims will facilitate, encourage and thus "result in" such use and administration of the distributed product as is contemplated in the second step of the independent claims, *i.e.*, safe use of a medicine in seriously ill patients. The claims are not directed to a method of distributing a product that will not be used. Indeed, the independent claims, as amended, now state that the medical provider is "responsible for treating a plurality of patients including neonates with hypoxic respiratory failure, including some who do not have left ventricular dysfunction and who are not dependent on right-to-left shunting of blood." Applicants are not claiming a method of "Here, take this nitric oxide gas source, but do not do anything with it," nor anything that resembles that description. Therefore, whether such a hypothetical claim would be patent eligible is not at issue.

The Office action also states: **"Furthermore, the step of providing a source of nitric oxide gas (or the gas itself) is extra-solution activity, not explicitly linked (or necessary) for the performance of the 'critical' steps of determining when a warning should be generated."** Again, Applicants respectfully disagree. The opinions expressed in that sentence are apparently based on a reading of the independent claims as including steps of "**determining when a warning should be generated**," steps the Office contends are "critical." However, *no such steps appear in the claim*. There is nothing in the claims that could be interpreted as requiring "**determining when a warning should be generated**." The independent claims recite "*providing*" a first warning and "*providing*" a second warning, not "determining when" or whether to do so. This is not a situation in which applicants are attempting to claim a formula or algorithm for "determining" or "solving" something. Since the claims don't involve arriving at

a "solution," the term "extra-solution activity" has no relevance to the independent claims, and no step of these claims can be dismissed on that basis.

Focusing on the actual language of claim 1, one sees that claim 1 is drawn to "a method of distributing a pharmaceutical product." Supplying the product (i.e., a source of nitric oxide gas) to a medical provider is *without a doubt* fundamental to the claimed method of distributing the product—not "extra-solution" nor "extra"-anything. And, since distribution of a pharmaceutical product in the U.S. requires that dosage information and warnings about any contraindications and safety risks be provided to medical providers along with the products, the provision of such information and warnings along with the product itself is also critical to the claimed method of distributing the product. Thus, there is no basis whatsoever to argue that any step is not "critical" and can be ignored for purposes of determining whether the claim qualifies as patent-eligible. All steps are integral to the method of distributing a product as presently claimed. Excluding any one would be purely arbitrary, and therefore unjustified.

As a final argument in support of the rejection of the independent claims, the Office action asserts, "**The steps of providing first and second warnings encompass providing a label or are thought processes and are not necessarily active steps. Therefore, the independent claims do not meet the requirements of 35 USC 101.**" Applicant agrees that the steps of providing the first and second warnings encompass providing a label that recites such warnings, but disagrees that these steps could be characterized as "thought processes." The two "warning" steps recite "**providing a first/second warning to the medical provider....**" The form in which the warnings are provided is not specified in the claim. Whether the providing is accomplished by providing a label or seminar or website or advertisement or otherwise, "providing to a medical provider" always requires that the warning be "provided"—i.e., transmitted or otherwise made available by one entity to another, the latter being a medical provider. "Providing" as used in the present claims is necessarily an active step that cannot be accomplished by merely thinking, so cannot be characterized as a "thought process." The Office does not explain how it could be that a label (or anything else) could be "provided" to a medical

provider merely by thinking. Absent such an explanation, acknowledgement that none of the steps of the independent claims is a "thought process" is respectfully requested.

In sum, the independent claims are drawn to methods of distributing a pharmaceutical product, with specified steps of supplying a source of nitric oxide gas, informing a medical provider about a specific dosage, and providing certain very specific warnings. The Office's assertion that the claims "could result in nothing more than warning a medical provider NOT to administer gas" does not accurately reflect the language of the claims, so is not a valid basis for determining whether the claims are drawn to patent-eligible subject matter. Practice of the claimed method steps will result in a source of nitric oxide gas being supplied to a medical provider. It will also result in the medical provider's being informed of a recommended dose for treatment of neonates with hypoxic respiratory failure and being provided with two warnings that facilitate the proper exercise of medical judgment and administration of nitric oxide gas to appropriate patients in an appropriate amount. Upon examination of all of the actual claim language, it is evident that the independent claims do not encompass "mental processes," do not contain steps of "determining" anything, and do not have steps that can be dismissed as "thought processes" or "extra-solution activity." There is therefore no basis for rejecting the independent claims as encompassing subject matter that is not patent-eligible.

B. Dependent claims

The logic set forth above applies equally to the dependent claims. Thus, each of the dependent claims qualifies as patent-eligible regardless of the nature of the limitations stated in the respective dependent claim. In addition, many of the dependent claims include limitations that provide further arguments separately supporting patent-eligibility, as explained below.

Although all of the claims stand rejected under § 101 as directed to non-statutory subject matter, the sole reason the Office action gives for rejecting any of the dependent claims is the following:

> The dependent claims that may recite an active step such as "perform at least one diagnostic process" are also rejected under 35 USC 101 because MPEP 2106 states: "A

> claim that covers both statutory and non-statutory embodiments (under the broadest reasonable interpretation of the claim when read in light of the specification and in view of one skilled in the art) embraces subject matter that is not eligible for patent protection and therefore is directed to non-statutory subject matter. Such claims fail the first step and should be rejected under 35 U.S.C. 101, for at least this reason." (emphasis added)

The Office's stated reason for rejecting the dependent claims thus applies on its face solely to the dependent claims "that may recite an active step." The Office does not specify exactly which dependent claims the Office believes "may recite an active step," other than to say that "perform at least one diagnostic process" qualifies as an "active step." This or a comparable step can be found in several dependent claims, including claim 7. Applicant will begin by discussing claim 7.

Claim 7 depends from claim 1, adding further steps including "performing at least one diagnostic process to identify a neonate patient who has hypoxic respiratory failure and is a candidate for 20 ppm inhaled nitric oxide treatment...." The above-quoted passage from the Office action acknowledges that this step qualifies as an "active step," but nevertheless rejects the claims containing such a step on the theory that such a claim "covers both statutory and non-statutory embodiments."

This rationale is not understood. First, regardless of the presence or absence of "active steps," *all* embodiments of *all* of the present claims are unquestionably "statutory subject matter." There are four categories of statutory subject matter listed in 35 USC § 101 as being eligible for patenting: process, machine, manufacture, and composition of matter. See § 101 and MPEP 2106.I. All of the present claims are drawn to methods (another term for "process"), so all *by definition* qualify as statutory subject matter. The term "statutory embodiment" as used in the text from MPEP 2106 quoted in the Office action refers to an embodiment that can be characterized as falling within one of the four categories of statutory subject matter. A "non-statutory embodiment" is an embodiment that does not fall into one of the four categories, i.e., is not a process or machine or manufacture or composition of matter. (*See* the full text of MPEP 2106.I (entitled "The Four Categories of Statutory Subject Matter"), which is the portion of 2106 from which the Office derived the quoted text.) Since *all* embodiments of *all* of the

present claims are methods, *all* embodiments qualify as statutory embodiments, and the quoted passage from the MPEP does not provide a reason to reject any of the present claims. It is simply irrelevant.

Second, in expressing a concern that some embodiments of claim 7 are not patent-eligible despite the presence in this claim of what the Examiner agrees is an active step, the Examiner seems to be opining that some embodiments of claim 7 do not encompass that active step. Applicant notes that an "embodiment" of a claim must meet *all* of the limitations of the claim. Something that meets fewer than all of the limitations of the claim is not covered by the claim, and so is not an "embodiment" of the claim. Accordingly, in order for a given method to constitute an "embodiment" of claim 7, the method would *have* to include the step of performing at least one diagnostic process (as well as all of the other steps recited in claim 7 *and* all of the steps recited in claim 1). None of these steps is optional. The Office has implicitly acknowledged that an embodiment that includes a step of performing at least one diagnostic process would by definition include an active step and so would be patent-eligible. Since *all* embodiments of claim 7 *must* include a step of performing at least one diagnostic process (otherwise they are not "embodiments" of claim 7), it follows that *all* embodiments of claim 7 qualify as patent-eligible.

If the Examiner intends to continue to reject claim 7, he is respectfully asked to explain how it would be possible to have an embodiment of claim 7 that lacks the required step of performing at least one diagnostic process.

If the Examiner is interpreting MPEP 2106 to mean that a claim that includes both "active" and "mental" steps does not qualify as patent-eligible because of the presence of the "mental" steps, he is asked to reconsider that position. It is certainly not what MPEP 2106 says. Furthermore, even if the Office continues to view claim 1 (from which claim 7 depends) as including one or more mental steps (a view that Applicant does not share), this is not a basis for rejecting claim 7. U.S. law does not prohibit the inclusion of one or more mental steps in a claim. *Classen Immunotherapies, Inc. v. Biogen IDEC*, 659 F.3d 1057, 1065 (Fed. Cir. 2011). The Examiner has acknowledged that the "performs at least one diagnostic process" step of

claim 7 qualifies as active. Accordingly, there is no legitimate basis to reject claim 7, regardless of whether independent claim 1 is or isn't viewed as patent-eligible.

Dependent claims 8, 17, 18, and 26 contain a "performs at least one diagnostic process" step similar to that found in claim 7. Claim 30 is worded differently: "performs echocardiography to identify a neonate patient who is a candidate for inhaled nitric oxide treatment." The rationale discussed above for claim 7 would also apply to each of claims 8, 17, 18, 26, and 30, as well as to their dependent claims 9, 10, 19, 20, 31, and 32.

Independent of the "diagnostic process/echocardiography" limitations discussed above, claims 7, 8, 17, 18, 26, and 30 (as amended) and their dependent claims also include treatment steps that certainly qualify as "active" steps.

Other dependent claims that contain indisputably "active" steps include claims 2, 4, 12, 14, 22, 24, 28, and 29. For example, claims 2, 12, 22, and 28 require "generating the source of nitric oxide gas prior to supplying the source to the medical provider." Claims 4, 14, 24, and 29 require more specifically "generating the source of nitric oxide gas by a method comprising compressing nitric oxide and nitrogen gases under high pressure, prior to supplying the source to the medical provider." By definition, all embodiments of each of claims 2, 4, 12, 14, 22, 24, 28, and 29 include an overtly active step, so these dependent claims cannot be characterized as covering embodiments that do not include an active step. Further, all embodiments of these claims are methods (processes), which is one of the four categories of statutory subject matter, so these claims cannot be characterized as encompassing any non-statutory embodiments.

Thus, regardless of the ultimate disposition of the independent claims, there is no legitimate basis for rejecting dependent claims 2, 4, 7-10, 12, 14, 17-20, 22, 24, 26, and 28-32 under § 101.

CONCLUSION

Applicant submits that all of the claims are in condition for allowance, and such action is respectfully requested. If a telephone conference would be helpful, the Examiner is invited to

telephone the undersigned at 808 986 0300 (if before April 22, 2013) or 617 521 7037 (if after April 29, 2013).

It is believed that no fees are due. Apply any necessary charges or credits to deposit account 06-1050, referencing the above attorney docket number.

Respectfully submitted,

Date: April 2, 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

23010433.doc

Electronic Acknowledgement Receipt	
EFS ID:	15410896
Application Number:	13683236
International Application Number:	
Confirmation Number:	5655
Title of Invention:	METHODS OF DISTRIBUTING A PHARMACEUTICAL PRODUCT COMPRISING NITRIC OXIDE GAS FOR INHALATION
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:	26047-0003006
Receipt Date:	02-APR-2013
Filing Date:	21-NOV-2012
Time Stamp:	14:39:31
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		response_26047_0003006.pdf	157388 2b48639cccd0525406ba415ea5b859146c3e3090	yes	23

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Amendment/Req. Reconsideration-After Non-Final Reject	1	2
	Claims	3	12
	Applicant Arguments/Remarks Made in an Amendment	13	23
Warnings:			
Information:			
	Total Files Size (in bytes):	157388	

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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.

PTO/SB/06 (07-06)
Approved for use through 1/31/2007. OMB 0651-0032
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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 13/683,236	Filing Date 11/21/2012	☐ To be Mailed

APPLICATION AS FILED – PART I

	(Column 1)	(Column 2)	SMALL ENTITY ☐		OR	OTHER THAN SMALL ENTITY	
FOR	NUMBER FILED	NUMBER EXTRA	RATE ($)	FEE ($)		RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =		OR	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =			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 $250 ($125 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			TOTAL	

APPLICATION AS AMENDED – PART II

		(Column 1)		(Column 2)	(Column 3)	SMALL ENTITY		OR	OTHER THAN SMALL ENTITY	
	04/02/2013	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)		RATE ($)	ADDITIONAL FEE ($)
AMENDMENT	Total (37 CFR 1.16(i))	* 30	Minus	** 30	= 0	X $ =		OR	X $80=	0
	Independent (37 CFR 1.16(h))	* 4	Minus	***4	= 0	X $ =		OR	X $420=	0
	☐ 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	**0**

		(Column 1)		(Column 2)	(Column 3)					
		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)		RATE ($)	ADDITIONAL FEE ($)
AMENDMENT	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 number found in the appropriate box in column 1.

Legal Instrument Examiner:
/DELEACHES YOUNG/

This collection of information is required by 37 CFR 1.16. 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, 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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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	13683236
Filing Date	2012-11-21
First Named Inventor	Baldassarre
Art Unit	1613
Examiner Name	Ernst V. Arnold
Attorney Docket Number	26047-0003006

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.	

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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	20020185126		2002-12-12	Krebs	
	2	20030131848		2003-07-17	Stenzler	

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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]

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	13683236
	Filing Date	2012-11-21
	First Named Inventor	Baldassarre
	Art Unit	1613
	Examiner Name	Ernst V. Arnold
	Attorney Docket Number	26047-0003006

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NON-PATENT LITERATURE DOCUMENTS Remove

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]
	1	Autorisation De Mise Sur Le Marche for VasoKINOX 450 ppm mole/mole issued by the Belgian Federal Agency for Drug and Medical Products (BE 320336), dated 14/07/2008 (37 pages, including English translation)	☒
	2	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)	☐
	3	Communication from Canadian Intellectual Property Office dated March 19, 2013, enclosing Protest from Robic regarding Canadian patent application no. 2,671,029 (42 pages)	☐
	4	Hess, "Heliox and Inhaled Nitric Oxide," Mechanical Ventilation, Chapter 28 (2001), pages 454-480	☐

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EXAMINER SIGNATURE

Examiner Signature		Date Considered	

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

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

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	13683236
	Filing Date	2012-11-21
	First Named Inventor	Baldassarre
	Art Unit	1613
	Examiner Name	Ernst V. Arnold
	Attorney Docket Number	26047-0003006

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)	2013-04-12
Name/Print	Janis K. Fraser	Registration Number	34819

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

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

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:	13683236
Filing Date:	21-Nov-2012
Title of Invention:	METHODS OF DISTRIBUTING A PHARMACEUTICAL PRODUCT COMPRISING NITRIC OXIDE GAS FOR INHALATION
First Named Inventor/Applicant Name:	James S. Baldassarre
Filer:	Janis K. Fraser/Nancy Bechet
Attorney Docket Number:	26047-0003006
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:	15503675
Application Number:	13683236
International Application Number:	
Confirmation Number:	5655
Title of Invention:	METHODS OF DISTRIBUTING A PHARMACEUTICAL PRODUCT COMPRISING NITRIC OXIDE GAS FOR INHALATION
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:	26047-0003006
Receipt Date:	12-APR-2013
Filing Date:	21-NOV-2012
Time Stamp:	13:52:57
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	134
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	Information Disclosure Statement (IDS) Form (SB08)	SB08_26047_0003006.pdf	612654 8f664b317b74848837fbc26c7d3c6d48f7090238	no	4
Warnings:					
Information:					
2	Non Patent Literature	ProtestRobic.pdf	4045379 24008447a33d1b35e43c82f384d090af5a2ab737	no	42
Warnings:					
Information:					
3	Non Patent Literature	ProtestTorys.pdf	5472833 ef4a7327814f284e845a869b1e8aa57494904946	no	36
Warnings:					
Information:					
4	Non Patent Literature	Hess.pdf	5443748 9d3b97f03c1d9a306d2fc4221eeda6c4e7aa2277	no	28
Warnings:					
Information:					
5	Non Patent Literature	frenchrefenglishtrans.pdf	2291043 d71ea21c6061443f110143b3c49acabecaee6b99	no	37
Warnings:					
Information:					
6	Fee Worksheet (SB06)	fee-info.pdf	30464 39f5f3ee99a4f53f944d6ced745b755b7f592c30	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	17896121		

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.
13/683,236	11/21/2012	James S. Baldassarre	26047-0003006	5655

94169 7590 04/17/2013
Fish & Richardson PC
P.O.Box 1022
minneapolis, MN 55440

EXAMINER	
ARNOLD, ERNST V	
ART UNIT	PAPER NUMBER
1613	
MAIL DATE	DELIVERY MODE
04/17/2013	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.

Applicant-Initiated Interview Summary	**Application No.** 13/683,236	**Applicant(s)** BALDASSARRE ET AL.	
	Examiner MARJORIE MORAN	**Art Unit** 1631	

All participants (applicant, applicant's representative, PTO personnel):

(1) *MARJORIE MORAN*. (3)_____.

(2) *JANIS FRASER*. (4)_____.

Date of Interview: *13 March 2013*.

Type: ☒ Telephonic ☐ Video Conference
☐ Personal [copy given to: ☐ applicant ☐ applicant's representative]

Exhibit shown or demonstration conducted: ☐ Yes ☒ No.
If Yes, brief description: _____.

Issues Discussed ☒101 ☐112 ☐102 ☐103 ☐Others
(For each of the checked box(es) above, please describe below the issue and detailed description of the discussion)

Claim(s) discussed: *1,4 and 7*.

Identification of prior art discussed: *NONE*.

Substance of Interview
(For each issue discussed, provide a detailed description and indicate if agreement was reached. Some topics may include: identification or clarification of a reference or a portion thereof, claim interpretation, proposed amendments, arguments of any applied references etc...)

Attorney Fraser asked whether amending claim 1 to recite "supplying" a source of gas would overcome the rejection under 35 USC 101. Examiner Moran agreed that supplying could be interpreted to be supplying a canister (i.e. a physical object); however, she also stated that this was not a transformation of matter, and that the limitation would still encompass having a canister in a room along with a set of instructions, and would therefore still encompass an abstract idea (e.g. recognizing that the canister exists, and thinking about what to do with it). There was discussion about whether actually generating the gas (e.g. as in claim 4) constituted a transformation of matter, and whether active steps of administering the gas and/or performing a diagnostic assay would overcome the 101 rejection. Ms. Fraser and Examiner Moran discussed possible claim language, but no particular suggestions were made and no specific agreements were reached .

Applicant recordation instructions: The formal written reply to the last Office action must include the substance of the interview. (See MPEP section 713.04). If a reply to the last Office action has already been filed, applicant is given a non-extendable period of the longer of one month or thirty days from this interview date, or the mailing date of this interview summary form, whichever is later, to file a statement of the substance of the interview

Examiner recordation instructions: Examiners must summarize the substance of any interview of record. A complete and proper recordation of the substance of an interview should include the items listed in MPEP 713.04 for complete and proper recordation including the identification of the general thrust of each argument or issue discussed, a general indication of any other pertinent matters discussed regarding patentability and the general results or outcome of the interview, to include an indication as to whether or not agreement was reached on the issues raised.

☐ Attachment

	/Marjorie Moran/ Supervisory Patent Examiner, Art Unit 1631

Summary of Record of Interview Requirements

Manual of Patent Examining Procedure (MPEP), Section 713.04, Substance of Interview Must be Made of Record
A complete written statement as to the substance of any face-to-face, video conference, or telephone interview with regard to an application must be made of record in the application whether or not an agreement with the examiner was reached at the interview.

Title 37 Code of Federal Regulations (CFR) § 1.133 Interviews
Paragraph (b)

In every instance where reconsideration is requested in view of an interview with an examiner, a complete written statement of the reasons presented at the interview as warranting favorable action must be filed by the applicant. An interview does not remove the necessity for reply to Office action as specified in §§ 1.111, 1.135. (35 U.S.C. 132)

37 CFR §1.2 Business to be transacted in writing.
All business with the Patent or Trademark Office should be transacted in writing. The personal attendance of applicants or their attorneys or agents at the Patent and Trademark Office is unnecessary. The action of the Patent and Trademark Office will be based exclusively on the written record in the Office. No attention will be paid to any alleged oral promise, stipulation, or understanding in relation to which there is disagreement or doubt.

The action of the Patent and Trademark Office cannot be based exclusively on the written record in the Office if that record is itself incomplete through the failure to record the substance of interviews.

It is the responsibility of the applicant or the attorney or agent to make the substance of an interview of record in the application file, unless the examiner indicates he or she will do so. It is the examiner's responsibility to see that such a record is made and to correct material inaccuracies which bear directly on the question of patentability.

Examiners must complete an Interview Summary Form for each interview held where a matter of substance has been discussed during the interview by checking the appropriate boxes and filling in the blanks. Discussions regarding only procedural matters, directed solely to restriction requirements for which interview recordation is otherwise provided for in Section 812.01 of the Manual of Patent Examining Procedure, or pointing out typographical errors or unreadable script in Office actions or the like, are excluded from the interview recordation procedures below. Where the substance of an interview is completely recorded in an Examiners Amendment, no separate Interview Summary Record is required.

The Interview Summary Form shall be given an appropriate Paper No., placed in the right hand portion of the file, and listed on the "Contents" section of the file wrapper. In a personal interview, a duplicate of the Form is given to the applicant (or attorney or agent) at the conclusion of the interview. In the case of a telephone or video-conference interview, the copy is mailed to the applicant's correspondence address either with or prior to the next official communication. If additional correspondence from the examiner is not likely before an allowance or if other circumstances dictate, the Form should be mailed promptly after the interview rather than with the next official communication.

The Form provides for recordation of the following information:
- Application Number (Series Code and Serial Number)
- Name of applicant
- Name of examiner
- Date of interview
- Type of interview (telephonic, video-conference, or personal)
- Name of participant(s) (applicant, attorney or agent, examiner, other PTO personnel, etc.)
- An indication whether or not an exhibit was shown or a demonstration conducted
- An identification of the specific prior art discussed
- An indication whether an agreement was reached and if so, a description of the general nature of the agreement (may be by attachment of a copy of amendments or claims agreed as being allowable). Note: Agreement as to allowability is tentative and does not restrict further action by the examiner to the contrary.
- The signature of the examiner who conducted the interview (if Form is not an attachment to a signed Office action)

It is desirable that the examiner orally remind the applicant of his or her obligation to record the substance of the interview of each case. It should be noted, however, that the Interview Summary Form will not normally be considered a complete and proper recordation of the interview unless it includes, or is supplemented by the applicant or the examiner to include, all of the applicable items required below concerning the substance of the interview.

A complete and proper recordation of the substance of any interview should include at least the following applicable items:
1) A brief description of the nature of any exhibit shown or any demonstration conducted,
2) an identification of the claims discussed,
3) an identification of the specific prior art discussed,
4) an identification of the principal proposed amendments of a substantive nature discussed, unless these are already described on the Interview Summary Form completed by the Examiner,
5) a brief identification of the general thrust of the principal arguments presented to the examiner,
   (The identification of arguments need not be lengthy or elaborate. A verbatim or highly detailed description of the arguments is not required. The identification of the arguments is sufficient if the general nature or thrust of the principal arguments made to the examiner can be understood in the context of the application file. Of course, the applicant may desire to emphasize and fully describe those arguments which he or she feels were or might be persuasive to the examiner.)
6) a general indication of any other pertinent matters discussed, and
7) if appropriate, the general results or outcome of the interview unless already described in the Interview Summary Form completed by the examiner.

Examiners are expected to carefully review the applicant's record of the substance of an interview. If the record is not complete and accurate, the examiner will give the applicant an extendable one month time period to correct the record.

Examiner to Check for Accuracy

If the claims are allowable for other reasons of record, the examiner should send a letter setting forth the examiner's version of the statement attributed to him or her. If the record is complete and accurate, the examiner should place the indication, "Interview Record OK" on the paper recording the substance of the interview along with the date and the examiner's initials.

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/683,236	11/21/2012	James S. Baldassarre	26047-0003006	5655

94169 7590 04/24/2013
Fish & Richardson PC
P.O.Box 1022
minneapolis, MN 55440

EXAMINER	
ARNOLD, ERNST V	
ART UNIT	PAPER NUMBER
1613	
MAIL DATE	DELIVERY MODE
04/24/2013	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. 13/683,236	Applicant(s) BALDASSARRE ET AL.	
	Examiner ERNST ARNOLD	Art Unit 1613	AIA (First Inventor to File) Status No

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

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* 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 *4/2/13*.

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

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

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

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

Disposition of Claims

5)☒ Claim(s) *1,2,4 and 6-32* 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) *1,2,4 and 6-32* is/are rejected.

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

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

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

Application Papers

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

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

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

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

Priority under 35 U.S.C. § 119

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

Certified copies:

a)☐ All b)☐ Some * c)☐ None of the:

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

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

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

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

Interim copies:

a)☐ All b)☐ Some c)☐ None of the: Interim copies of the priority documents have been received.

Attachment(s)

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

2) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/12/13*.

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

4) ☐ Other: _____.

DETAILED ACTION

Claims 31 and 32 are new. Claims 3 and 5 have been cancelled. Claims 1, 2, 4 and 6-32 are pending and under examination. Applicant has furnished an IDS with relevant art applied below. Consequently, this Action is FINAL.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on 4/12/13 was filed after the mailing date of the office action on 1/3/13. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Priority

The Examiner notes that there is no disclosure of, for example, "A method of distributing a pharmaceutical product" as instantly claimed in any of the parent documents. Consequently, for application of prior art, Applicant is only afforded the filing date of the instant application which is 11/21/12.

Withdrawn rejections:

Applicant's amendments and arguments filed 4/2/13 are acknowledged and have been fully considered. The Examiner has re-weighed all the evidence of record. Any rejection and/or objection not specifically addressed below is herein withdrawn.

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

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1, 2, 6, 11, 12, 13, 15, 16, 21-23, 25, 27 and 28 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. The independent claims are directed to mental processes which are non-statutory subject matter. In claims 1, 11, 21 and 27, for example, the step of "supplying a source of nitric oxide gas" is considered to be no different from the previous "providing", as evidenced by the Merriam-Webster Dictionary Definition (attached) meaning "to make available for use: provide", and still encompasses 'supplying' a catalog or website for the artisan to read and make a choice and it is not necessarily an active step. The step of supplying a source of nitric oxide gas (or the gas itself) is also extra-solution activity, not explicitly linked (or necessary) for the performance of the "critical" steps of determining when a warning should be generated. The nitric oxide gas is never administered in the method and therefore the step of "supplying" is extra-solution activity and does not impose meaningful limits on the execution of the subsequent steps which weighs heavily in favor against eligibility. The steps of informing and providing first and second warnings encompass providing a label or are thought processes of

conveying information and are not necessarily active steps and amounts to nothing more than the artisan reading a label which is a mental process. Therefore, the independent claims do not meet the requirements of 35 USC 101 and the dependent claims rejected also do not provide for a patent eligible subject matter.

Please note that the Examiner has again consulted with the Technology Centers resident expert Quality Assurance Specialist on 35 USC 101 to assist in the claim analysis and drafting of this rejection.

Response to Arguments:

The Examiner has consulted with TC1600's 101 specialist and carefully considered all of Applicant's arguments but has found them unpersuasive. Applicant's arguments concerning 'providing' are moot in view of the new ground of rejection. Applicant argues that the processes are not directed to "mental processes" but active steps that cannot be performed merely by thinking. It remains the Examiner's position that a label can provide the warning and be read to inform or provide information to the reader and therefore not active step is required by the practitioner to 'provide' the warning. The step of "supplying" fails the patent eligible test for the reasons discussed above.

Applicant argues that U.S. law does not require that the instant method include a step of administering the product. That it correct; but U.S. law requires that the claims be eligible for patentability and the instant claims fail that analysis.

Applicant argues that is not true that the entire claim could result in nothing more than warning a medical provider NOT to administer gas. The Examiner cannot agree because no gas is ever positively administered in the independent claims.

Applicant argues that it is implicit in the Office Action that the third and fourth warning steps convert the claimed method into mere instruction "not to do anything." The Examiner cannot agree because nothing is done with the nitric oxide gas. One merely reads some directions, performs some mental processing and then does nothing with the gas. Active treatment of patients with NO gas is not a limitation of the independent claims and Applicant's arguments on this point are not persuasive.

Applicant disagrees that providing a source of nitric oxide gas is extra-solution activity because there are no critical steps of determining when a warning should be generated. The Examiner disagrees because the warnings provide criteria for determining the patients to avoid treatment. This argument is not persuasive.

Applicant argues that supplying the product is fundamental to a method of distributing the product. That is not at issue. The term 'distributing' is not an active method step of the claim but rather merely language in the claim preamble. What is at issue is how the step of 'supplying' imposes meaningful limits on the execution of the claimed method steps. Since administration of the NO gas is not required in the subsequent steps then the step of 'supplying' is irrelevant to the execution of the other method steps.

Applicant disagrees that the warnings could be characterized as thought processes and argues that 'providing' is necessarily an active step that cannot be

accomplished by merely thinking and so cannot be characterized as a 'thought process'. The Examiner cannot agree. There is no step of actually doing anything with the warning provided and therefore it remains the Examiner's position that the instant claim language is not patent eligible subject matter.

None of Applicant's arguments are persuasive.

Claim Rejections - 35 USC § 103

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

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

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

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

Claims 1, 2, 4 and 6-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over VasoKINOX (IDS filed 4/12/13; 07/2008, 37 pages) in view of Kazerooni et al. (Cardiopulmonary Imaging 2004, Lippincott Williams & Wilkins, pages 234 and 236 in part) and Loh et al. (Circulation 1994, 90, 2780-2785) and Leo (Primary Care Companion J Clin Psychiatry 1999, 1:5; pp 131-141) and Himashree et al.

(Current Science 2003, 85, 5, pages 607-614) and McLaughlin et al. (Circulation, 2006, 114, 1417-1431).

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

Applicant claims a method of distributing a pharmaceutical product.

Determination of the scope and content of the prior art

(MPEP 2141.01)

VasoKINOX teaches methods of distributing the pharmaceutical product VasoKINOX (pages 19-21 of 37) by supplying a cylinder of mixed nitrogen/nitric oxide under a pressure of 200 bar (pages 21, 23, 33 and 36 of 37) and other devices such as ventilators (page 24 of 37) and treating pulmonary hypertension, a form of hypoxic respiratory failure, which is a condition for which inhaled nitric oxide is indicated, via inhaled nitric oxide gas from a cylinder in adults and children with a mean pulmonary arterial pressure to mean systemic pressure ratio greater than or equal to 50% and/or pulmonary vascular resistance greater than or equal to 5 UWood (pages 23 and 32 of

37) with the warnings/prescribing information to not use VasoKINOX in the event of these distinct contraindications/warnings:

- Left ventricular dysfunction (LVD);
- All forms of pulmonary arterial hypertension due to pulmonary hyper-flow; and
- Newborns dependent on a right-to-left shunt (pages 25 and 32 of 37). Newborns reads on neonatal patients.

VasoKINOX teaches dosage recommendations of 20 ppm NO after dilution in an air/oxygen mixture (page 23 and 34 of 37, bottom) from cylinder of mixed nitrogen/nitric oxide under a high pressure of 200 bar (pages 21, 23, 33 and 36 of 37) and is marketed by AIR LIQUIDE (pages 20, 31 and 37 of 37). Note that the dosage recommendations appears in the same prescribing document with the warnings that is supplied to the medical provider. VasoKINOX warns of pulmonary edema (pages 27 and 35 of 37). VasoKINOX teaches how to transport the cylinders (page 30 of 37).

VasoKINOX teaches that NO is a vasodilator and reduces pulmonary vascular resistance which implicitly can create vascular hypotension (page 28 of 37).

Consequently, it is implicit in the disclosure of VasoKINEX for the medical provider to evaluate/make the decision on a case by case basis for the potential benefit of treating the patient with 20 ppm inhaled NO for the potential benefit vs. the potential risk of the warnings prior to treatment with inhaled nitric oxide and exclude any number of newborns who meet the exclusion criteria and thus avoid the risk of putting one or more of these patients at risk of pulmonary edema and administer VasoKINEX to any number of patients including newborns who pass the exclusion criteria. The only way to

determine if the patient meets the exclusion criteria is to perform at least one diagnostic test to ascertain if the condition is present. In other words, if the newborn is not dependent on right to left shunting of blood and does not have LVD then the medical provider makes the decision to treat the newborn with 20 ppm inhaled NO. It is also implicit that the nitric oxide gas source was generated prior to supplying to the medical provider by being compressing under high pressure a mixture of nitric oxide and nitrogen gases into the cylinder otherwise one would not have a compressed gas cylinder generated for the medical provider.

Kazerooni et al. teach that PCWP is used to reflect left-sided heart function and is a reflection of left ventricular dysfunction (page 234). Kazerooni et al. teach that normal PCWP is 6-12 mm Hg and as the PCWP rises to 18-25 mm Hg, it exceeds the normal colloid osmotic pressure of blood and a fluid transudate develops in the lung interstitium edema (page 236). Also note that Applicant teaches that normal upper limit of PCWP in children is 10-12 mm Hg and in adults is 15 mm Hg [0060]. Therefore the ordinary artisan in the cardiac field knows very well that a PCWP of greater than 20 mm Hg results in edema.

Loh et al. teach that inhalation of nitric oxide in patients with LVD can increase the pulmonary artery wedge pressure (synonymous with PCWP) as measured by echocardiography (Abstract and Figure 2 and page 2782 right column). Loh et al. teach that the more severe LV dysfunction was present in the patients who had the largest increases in pulmonary artery wedge pressure with inhaled NO (bottom right column page 2782). Indeed, Loh et al. defined a group of patients with a pulmonary artery

wedge pressure of ≥18 mm Hg indicating LV failure had a greater effect of inhaled NO (page 2784, left column).

Himashree et al. teach INO for persistent pulmonary hypertension of the newborn and that adverse effects of inhaled NO include systemic hypotension and methaemoglobinemia and that infants "who receive INO therapy should be monitored according to protocols designed to avoid the potential toxic effects associated with INO administration" (Abstract and pages 610-611, Adverse effects of INO).

Leo teaches that primary care physicians can make treatment decisions based on assessment of benefits and risks as shown in Table 1 (page 133) below:

Table 1. Standards for Capacity Assessment as a Function of Patient Decision and Benefits/Risks Associated With an Intervention[a]

	Intervention	
Decision	Likely Beneficial Outcome and/or Low Risk	Likely Poor Outcome and/or High Risk
Accept intervention	Low standard for capacity assessment	High standard for capacity assessment
Refuse intervention	High standard for capacity assessment	Low standard for capacity assessment

[a]Adapted from Roth et al.[3]

Leo teaches understanding the natural course of the Medical condition; understanding the proposed treatment intervention; understanding the risks and potential benefits; understanding the consequences of treatment or intervention refusal and understanding viable alternatives (page 135).

McLaughlin et al. teach that edema is a symptom of pulmonary arterial hypertension (PAH) (Table 2, page 1420). McLaughlin et al. also teach a diagnostic algorithm using, for example, an echocardiogram determination of left heart disease and

that Doppler echocardiography is the essential screening tool for the presence of PAH. (Figure 3, page 1422, right column and page 1423, Figure 4C).

Ascertainment of the difference between the prior art and the claims

(MPEP 2141.02)

1. The difference between the instant application and VasoKINOX is that VasoKINOX do not expressly teach that inhaled NO may/could increase PCWP leading to a potential risk of pulmonary edema. This deficiency in VasoKINOX is cured by the teachings of Kazerooni et al. and Loh et al.

2. The difference between the instant application and VasoKINOX is that VasoKINOX do not expressly teach determining if the potential benefit of the treatment outweighs the potential risk described in the second warning and treating the patient with LVD with 20 ppm iNO or discontinuing treatment with iNO if pulmonary edema occurs. This deficiency in VasoKINOX is cured by the teachings of Kazerooni et al. and Loh et al. in further view of Leo.

3. The difference between the instant application and VasoKINOX is that VasoKINOX do not expressly teach performing echocardiography to identify a neonate who is a candidate for iNO treatment and discontinuing treatment due to hypotension or monitoring for evidence of an increase in PCWP or pulmonary edema during treatment. This deficiency in VasoKINOX is cured by the teachings of Kazerooni et al., Loh et al. and Leo in further view of Himashree et al. and McLaughlin et al.

Finding of prima facie obviousness

Rational and Motivation (MPEP 2142-2143)

1. It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to perform the method of VasoKINOX and teach that inhaled NO may/could increase PCWP leading to a potential risk of pulmonary edema**,** as suggested by Kazerooni et al. and Loh et al., and produce the instant invention.

One of ordinary skill in the art would have been motivated to do this because it is very well known in the art that a PCWP of greater than 20 mm Hg results in edema regardless of how the PCWP is increases and it is also very well known in the art that inhaled NO increases PCWP as taught by Loh et al. Therefore is obvious to teach/warn/instruct the artisan administering iNO therapy that inhaled NO may/could increase PCWP leading to a potential risk of pulmonary edema.

2. It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to perform the method of VasoKINOX and teach determining if the potential benefit of the treatment outweighs the potential risk described in the second warning and treating the patient with LVD with 20 ppm iNO or discontinuing treatment with iNO if pulmonary edema occurs**,** as suggested by Kazerooni et al., Loh et al., McLaughlin et al. and Leo, and produce the instant invention.

One of ordinary skill in the art would have been motivated to do this because it is common in the medical arts for the artisan administering the therapy to make

benefit/risk assessments on a case by case basis. Patients where the therapy is contraindicated by the distributer of the pharmaceutical product but left with no further options except death may have benefit from administration of iNO. This is a choice by the artisan and perfectly within the realm of an obvious decision by the artisan including the decision to terminate treatment at any time for any reason including if pulmonary edema occurs especially when the art warns of pulmonary edema as a potential adverse event. In the event that Applicant should take the position that the artisan would not administer the iNO to neonatal patients that meet the exclusion criteria of VasoKINOX, have left ventricular dysfuction consistent with a PCWP of greater than or equal to 20 mm Hg, because VasoKINOX teaches not to use the product under those conditions (left ventricular dysfuction/all forms of pulmonary arterial hypertension), it is the Examiner's position that the artisan in this art is not an automaton (See MPEP 2141.03) and in terms of the patients welfare administration of a therapy is a decision for the medical artisan and the family of the patient to determine and not the distributer of the pharmaceutical product. The distributer may make warnings but the medical artisan and the family of the patient may or may not abide by them depending on the risks and benefits and outcomes for the patient. Consequently, the medical practitioner may make the choice to disregard such warnings when the situation presents itself for the sake of the patient and not the distributer of the pharmaceutical product.

3. It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to perform the method of VasoKINOX and teach performing echocardiography to identify a neonate who is a candidate for iNO treatment

and discontinuing treatment due to hypotension or monitoring for evidence of an increase in PCWP or pulmonary edema during treatment**,** as suggested by Kazerooni et al. and Loh et al., Leo, McLaughlin et al. and Himashree et al., and produce the instant invention.

One of ordinary skill in the art would have been motivated to do this because as taught by Loh et al. and McLaughlin et al., echocardiography is an essential screening tool to assess the patient for left ventricular function, an exclusion criteria in the method of VasoKINOX, and Himashree et al. direct the artisan to monitor the patient for adverse events such as systemic hypotension and, as taught by Kazerooni et al. and Loh et al. and increase in PCWP over 20 mm Hg which would be indicative of edema which is a symptom of PAH as taught by Mclaughlin et al. and thus the ordinary artisan would be cognizant of this adverse event and monitor for it in at least one patient. Thus, it is obvious for the artisan to monitor for edema, hypotension and any other possible adverse event due to the administration of iNO for the patient's benefit and discontinue treatment due to the patient's hypotension or any other adverse event that places the patient's safety at risk. This is just common sense.

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

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of

ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Conclusion

No claims are allowed.

Applicant's submission of an information disclosure statement under 37 CFR 1.97(c) with the fee set forth in 37 CFR 1.17(p) on 4/2/13 prompted the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 609.04(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

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

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ERNST 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. 13/683,236	Applicant(s)/Patent Under Reexamination BALDASSARRE ET AL.	
	Examiner ERNST ARNOLD	Art Unit 1613	Page 1 of 2

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-			
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	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	Suppying [online] retrieved on 4/22/13 from: http://www.merriam-webster.com/dictionary/supplying 4 pages.
	V	McLaughlin et al. (Circulation, 2006, 114, 1417-1431).
	W	Himashree et al. (Current Science 2003, 85, 5, pages 607-614)
	X	Leo (Primary Care Companion J Clin Psychiatry 1999, 1:5; pp 131-141)

*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.

Notice of References Cited	Application/Control No. 13/683,236	Applicant(s)/Patent Under Reexamination BALDASSARRE ET AL.	
	Examiner ERNST ARNOLD	Art Unit 1613	Page 2 of 2

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
	A	US-			
	B	US-			
	C	US-			
	D	US-			
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	F	US-			
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	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	Kazerooni et al. (Cardiopulmonary Imaging 2004, Lippincott Williams & Wilkins, pages 234 and 236 in part)
	V	Loh et al. (Circulation 1994, 90, 2780-2785)
	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.

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	13683236
	Filing Date	2012-11-21
	First Named Inventor	Baldassarre
	Art Unit	1613
	Examiner Name	Ernst V. Arnold
	Attorney Docket Number	26047-0003006

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
/E.A./	1	5558083		1996-09-24	Bathe et al.	
/E.A./	2	5651358		1997-07-29	Briend et al.	
/E.A./	3	6142147		2000-11-07	Head et al.	
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/E.A./	1	20020185126		2002-12-12	Krebs	
/E.A./	2	20030131848		2003-07-17	Stenzler	
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	13683236
	Filing Date	2012-11-21
	First Named Inventor	Baldassarre
	Art Unit	1613
	Examiner Name	Ernst V. Arnold
	Attorney Docket Number	26047-0003006

	1							☐

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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]
/E.A./	1	Autorisation De Mise Sur Le Marche for VasoKINOX 450 ppm mole/mole issued by the Belgian Federal Agency for Drug and Medical Products (BE 320336), dated 14/07/2008 (37 pages, including English translation)	☒
/E.A./	2	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./	3	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./	4	Hess, "Heliox and Inhaled Nitric Oxide," Mechanical Ventilation, Chapter 28 (2001), pages 454-480	☐

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EXAMINER SIGNATURE

Examiner Signature	/Ernst Arnold/	Date Considered	04/17/2013

*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.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	13683236
	Filing Date	2012-11-21
	First Named Inventor	Baldassarre
	Art Unit	1613
	Examiner Name	Ernst V. Arnold
	Attorney Docket Number	26047-0003006

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)	2013-04-12
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.

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13683236	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

SEARCH NOTES		
Search Notes	Date	Examiner
consultation with QAS Majorie Moran on 101 issues and drafting of rejection	12/21/12	eva
consultation with TC1600 MMoran on 101 issues and claim rejections	4/19/13	eva
search update EAST all databases	4/22/13	eva

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

EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
S1	1	"20100330206".pn. and ((supply or supplying) and (medical adj provider) and responsible)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2013/04/12 14:50
S2	1	"20100330206".pn. and ((supply or supplying) and (medical adj provider) and responsible and (delivery with device))	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2013/04/12 14:51
S3	0	"20100330206".pn. and (source with ((compressed adj gas) or (delivery adj devicd)))	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2013/04/12 14:52
S4	1	"20100330206".pn. and (source with ((compressed adj gas) or (delivery adj device)))	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2013/04/12 14:52
S5	1	"20130078321".pn. and (source with ((compressed adj gas) or (delivery adj device)))	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2013/04/12 14:54
S6	1	"20100330206".pn. and ((compressed adj gas) or (delivery adj device))	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2013/04/12 14:57
S7	1	"20100331405".pn. and ((compressed adj gas) or (delivery adj device))	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2013/04/12 14:59
S8	0	"20130078321".pn. and (distribute or distributing)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2013/04/12 15:24
S9	0	"20100331405".pn. and (distribute or distributing)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2013/04/12 15:26
S10	0	"8431163".pn. and (distribute or distributing)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2013/04/12 15:28
S11	0	"20100330206".pn. and (distribute or distributing)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2013/04/12 15:29
S12	0	"13683236" and benefit and outweigh and potential	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2013/04/20 10:45

S13	1	"13683236" and (benefit with potential)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2013/04/20 10:45

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	: James S. Baldassarre et al.	Art Unit	: 1613
Serial No.	: 13/683,236	Examiner	: Ernst V. Arnold
Filed	: November 21, 2012	Conf. No.	: 5655

Title : METHODS OF DISTRIBUTING A PHARMACEUTICAL PRODUCT COMPRISING NITRIC OXIDE GAS FOR INHALATION

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

NOTICE OF APPEAL

Applicant hereby appeals to the Patent Trial and Appeal Board from the action dated April 24, 2013, finally rejecting claims 1, 2, 4, and 6-32.

The appeal fee and three-month extension of time fee are 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: October 23, 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

23109958.doc

Electronic Patent Application Fee Transmittal	
Application Number:	13683236
Filing Date:	21-Nov-2012
Title of Invention:	METHODS OF DISTRIBUTING A PHARMACEUTICAL PRODUCT COMPRISING NITRIC OXIDE GAS FOR INHALATION
First Named Inventor/Applicant Name:	James S. Baldassarre
Filer:	Janis K. Fraser/Rita Liston
Attorney Docket Number:	26047-0003006
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:				
Notice of Appeal	1401	1	800	800
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension - 3 months with $0 paid	1253	1	1400	1400
Miscellaneous:				
		Total in USD ($)		**2200**

Electronic Acknowledgement Receipt	
EFS ID:	17205259
Application Number:	13683236
International Application Number:	
Confirmation Number:	5655
Title of Invention:	METHODS OF DISTRIBUTING A PHARMACEUTICAL PRODUCT COMPRISING NITRIC OXIDE GAS FOR INHALATION
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:	26047-0003006
Receipt Date:	23-OCT-2013
Filing Date:	21-NOV-2012
Time Stamp:	13:51:05
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$2200
RAM confirmation Number	97
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	Notice of Appeal Filed	26047_0003006_not_app.pdf	60788 b0dfd6a1b5aa53d0e9d0b6528462aef65b7c499f	no	1
Warnings:					
Information:					
2	Fee Worksheet (SB06)	fee-info.pdf	32360 5f03e00d5225c36647e1e6ba376649ef02cb7a42	no	2
Warnings:					
Information:					
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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.

Attorney Docket No.: 26047-0003006
Client Ref. No.: 3000-US-0008DIV

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	: James S. Baldassarre	Art Unit	: 1613
Serial No.	: 13/683,236	Examiner	: Ernst V. Arnold
Filed	: November 21, 2012	Conf. No.	: 5655
Title	: METHODS OF DISTRIBUTING A PHARMACEUTICAL PRODUCT COMPRISING NITRIC OXIDE GAS FOR INHALATION		

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 that identifies 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: November 19, 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

23105515.doc

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	26047-0003006
	Application Number	13/683,236
Title of Invention	METHODS OF DISTRIBUTING A PHARMACEUTICAL PRODUCT COMPRISING NITRIC OXIDE GAS FOR INHALATION	
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.		

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:					
Address 1	~~1 Byron Court~~				
Address 2					

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	26047-0003006
	Application Number	13/683,236
Title of Invention	METHODS OF DISTRIBUTING A PHARMACEUTICAL PRODUCT COMPRISING NITRIC OXIDE GAS FOR INHALATION	

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**)	11/19/2013
First Name	Janis	Last Name	Fraser	Registration Number	34,819

Electronic Patent Application Fee Transmittal	
Application Number:	13683236
Filing Date:	21-Nov-2012
Title of Invention:	METHODS OF DISTRIBUTING A PHARMACEUTICAL PRODUCT COMPRISING NITRIC OXIDE GAS FOR INHALATION
First Named Inventor/Applicant Name:	James S. Baldassarre
Filer:	Janis K. Fraser/Rita Liston
Attorney Docket Number:	26047-0003006
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($)
Miscellaneous:				
Correction of Inventorship on Merits	1819	1	600	600
		Total in USD ($)		**600**

Electronic Acknowledgement Receipt	
EFS ID:	17438956
Application Number:	13683236
International Application Number:	
Confirmation Number:	5655
Title of Invention:	METHODS OF DISTRIBUTING A PHARMACEUTICAL PRODUCT COMPRISING NITRIC OXIDE GAS FOR INHALATION
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:	26047-0003006
Receipt Date:	19-NOV-2013
Filing Date:	21-NOV-2012
Time Stamp:	11:20:42
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$600
RAM confirmation Number	11971
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_0003006_Req_Corr_Inv.pdf	46669 aa8c31bb29422a96fcabf7adc3e3d3fee9d86a95	no	1
Warnings:					
Information:					
2	Application Data Sheet	26047_0003006_Supp_ADS.pdf	83454 7948ffd9a72aec323f144f5c00d270b3ec37e051	no	2
Warnings:					
Information:					
This is not an USPTO supplied ADS fillable form					
3	Fee Worksheet (SB06)	fee-info.pdf	30478 dca71423cb1b20b7c3cf82e98f404797e54ff0a4	no	2
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Information:					
		Total Files Size (in bytes):	160601		

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

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

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

Document code: WFEE

United States Patent and Trademark Office
Sales Receipt for Accounting Date: 11/22/2013

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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	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
13/683,236	11/21/2012	1613	2430	26047-0003006	30	4

CONFIRMATION NO. 5655

REPLACEMENT FILING RECEIPT

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

OC000000065176011

Date Mailed: 11/25/2013

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 DIV of 12/820,866 06/22/2010 ABN
which is a CON of 12/494,598 06/30/2009 ABN
This application 13/683,236
is a DIV of 13/651,660 10/15/2012 PAT 8431163
which is a CON of 12/821,041 06/22/2010 PAT 8293284
which is a CON of 12/494,598 06/30/2009 ABN

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

If Required, Foreign Filing License Granted: 12/04/2012
The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 13/683,236**
Projected Publication Date: Not Applicable

Non-Publication Request: No

Early Publication Request: No

Title

METHODS OF DISTRIBUTING A PHARMACEUTICAL PRODUCT COMPRISING NITRIC OXIDE GAS FOR INHALATION

Preliminary Class

424

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

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 (1-866-999-4258).

LICENSE FOR FOREIGN FILING UNDER

Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

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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

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PTO/SB/30 (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
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Request for Continued Examination (RCE) Transmittal

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

Application Number	13/683,236
Filing Date	November 21, 2012
First Named Inventor	James S. Baldassarre
Art Unit	1613
Examiner Name	Ernst V. Arnold
Attorney Docket Number	26047-0003006

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 Request for Prioritized Exam Track

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	December 23, 2013
Name (Print/Type)	Janis K. Fraser, Ph.D., J.D.	Registration No.	34,819

CERTIFICATE OF MAILING OR TRANSMISSION

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

Signature	/Rita M. Liston/		
Name (Print/Type)	Rita M. Liston	Date	12-23-2013

This collection of information is required by 37 CFR 1.114. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 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, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Mail Stop RCE, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

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):	13/683,236
Title of Invention:	METHODS OF DISTRIBUTING A PHARMACEUTICAL PRODUCT COMPRISING NITRIC OXIDE GAS FOR INHALATION		

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 December 23, 2013
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.

23126589.doc

Electronic Patent Application Fee Transmittal

Application Number:	13683236
Filing Date:	21-Nov-2012
Title of Invention:	METHODS OF DISTRIBUTING A PHARMACEUTICAL PRODUCT COMPRISING NITRIC OXIDE GAS FOR INHALATION
First Named Inventor/Applicant Name:	James S. Baldassarre
Filer:	Janis K. Fraser/Rita Liston
Attorney Docket Number:	26047-0003006

Filed as Large Entity

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Request for Prioritized Examination	1817	1	4000	4000
Pages:				
Claims:				
Miscellaneous-Filing:				
PROCESSING FEE, EXCEPT PROV. APPLS.	1830	1	140	140
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Miscellaneous:				
Request for Continued Examination	1801	1	1200	1200
		Total in USD ($)		**5340**

Electronic Acknowledgement Receipt	
EFS ID:	17740264
Application Number:	13683236
International Application Number:	
Confirmation Number:	5655
Title of Invention:	METHODS OF DISTRIBUTING A PHARMACEUTICAL PRODUCT COMPRISING NITRIC OXIDE GAS FOR INHALATION
First Named Inventor/Applicant Name:	James S. Baldassarre
Customer Number:	94169
Filer:	Janis K. Fraser/Joe Farrell
Filer Authorized By:	Janis K. Fraser
Attorney Docket Number:	26047-0003006
Receipt Date:	23-DEC-2013
Filing Date:	21-NOV-2012
Time Stamp:	16:59:18
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$5340
RAM confirmation Number	4919
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File Listing:

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

1	Non Patent Literature	CA_OA_04252013.pdf	381713 2c94f97c6ef42bd18175a02d3284334eacb5d7df	no	24
Warnings:					
Information:					
2	Non Patent Literature	Stewart_2009.pdf	6920015 112247ddb9008ccf1bdb4858114adecc34126e41	no	71
Warnings:					
Information:					
3	Non Patent Literature	26047_Preston_article.pdf	134131 7455f4767018ad4fc56d22ff949ba715a618f79c	no	4
Warnings:					
Information:					
4	Non Patent Literature	26047_bernasconi.pdf	1705494 214b0170180c8f1c61f3025dcffe48ab1cbfe75e	no	31
Warnings:					
Information:					
5	Non Patent Literature	26047_ltr_ids_ca_pto_080913.pdf	2625358 fbb43c91f795c23a1cc0a42783262f8b32468c75	no	51
Warnings:					
Information:					
6	Non Patent Literature	26047_NCT00626028_022808_28_ClinicalTrials_gov_Archive.pdf	43355 23202716bef23dac49d29796556912ebb068aa65	no	3
Warnings:					
Information:					
7	Non Patent Literature	McMullan.pdf	518350 1749ef78ea12a4ed2133d353c778be1d29b0d59f	no	7
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Information:					
8	Non Patent Literature	Clutton_Brock.pdf	414521 360b1a4d86639197f26b2f6b9edfe116bc98bcae	no	5
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Information:					
9	Non Patent Literature	Shiel.pdf	2279991 891e3c585e89c293beb623cf41c6938f6dff6b30	no	12
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10	Non Patent Literature	Weinberger.pdf	1597894 d2e727a6a6beff18daba1d80e4464f5dbb5ce2aa	no	15
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11	Non Patent Literature	Hayward.pdf	464364 de1ddc7107d589c55cde6e199d47d4fbccbe6412	no	11
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12	Non Patent Literature	Mourani.pdf	113655 cb350e9a6769f0f718d02f961b8609e37fe1494b	no	3
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13	Non Patent Literature	vasokinox_Public_Assessment_report.pdf	1083958 36393984519c68818fab8bcd74eb5b350973661e	no	34
Warnings:					
Information:					
14	Information Disclosure Statement (IDS) Form (SB08)	23096356.pdf	613323 70d60fa8ce3371745b725780e90a04be1a0ae05c	no	5
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.					
15		26047_0003006_Resp.pdf	7711648 972c7354e43f9bc734eb145baa825c12c431f74e	yes	309

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	After Final Consideration Program Request	1	1
	Specification	2	2
	Claims	3	10
	Applicant Arguments/Remarks Made in an Amendment	11	309

Warnings:	
Information:	

16	Request for Continued Examination (RCE)	26047_0003006_RCE.pdf	142407 8f4a50ced0b477deeb85a306f8138dfdc048881a	no	1
Warnings:					
This is not a USPTO supplied RCE SB30 form.					
Information:					
17	TrackOne Request	26047_0003006_Track_1.pdf	137403 0692daa2f2cd850ea98affa14276a0dc67ff1a95	no	1
Warnings:					
Information:					
18	Fee Worksheet (SB06)	fee-info.pdf	33665 1dfd034b4166c5ee4cb6e0856e9d47d7c41fb24e	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	26921245		

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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
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	13683236
Filing Date	2012-11-21
First Named Inventor	Baldassarre
Art Unit	1613
Examiner Name	Ernst V. Arnold
Attorney Docket Number	26047-0003006

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	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	13683236
	Filing Date	2012-11-21
	First Named Inventor	Baldassarre
	Art Unit	1613
	Examiner Name	Ernst V. Arnold
	Attorney Docket Number	26047-0003006

	12	Hayward et al., Inhaled nitric oxide in cardiology practice; Cardiovascular Research 43:628-638 (1999)	☐
	13	Mourani, et al., Left Ventricular Diastolic Dysfunction in Bronchopulmonary Dysplasia; J. of Pediatrics; 152:291-293 (2008)	☐
	14		☐
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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)		
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	Attorney Docket Number	26047-0003006

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)	2013-12-23
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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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	Art Unit	: 1613
Serial No.	: 13/683,236	Examiner	: Ernst V. Arnold
Filed	: November 21, 2012	Conf. No.	: 5655
Title	: METHODS OF DISTRIBUTING A PHARMACEUTICAL PRODUCT COMPRISING NITRIC OXIDE GAS FOR INHALATION		

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

AMENDMENT IN REPLY TO ACTION OF APRIL 17, 2013

This amendment is being filed with Exhibits A-F, a Request for Continued Examination, a request for prioritized examination under Track 1, and an Information Disclosure Statement. A Notice of Appeal with appropriate extension of time fees was filed on October 23, 2013, and a Request to Correct Inventorship was filed on November 19, 2013.

Please amend the above-identified application as follows:

Amendments to the Specification

Replace paragraph [0058] beginning at page 18 with the following amended paragraph:

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]] 124 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.

Replace paragraph [0064] on page 20 with the following amended paragraph:

In the INOT22 study, 10 of the total [[134]] 124 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.

Amendments to the Claims

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

Listing of Claims:

1. (Currently amended) A method of providing ~~distributing~~ a pharmaceutical product, the method comprising:

generating a cylinder containing compressed nitric oxide gas by a process comprising compressing nitric oxide and nitrogen gases under high pressure;

supplying the cylinder containing compressed ~~a source of~~ nitric oxide gas to a medical provider responsible for treating a plurality of neonates with hypoxic respiratory failure, including some who do not have left ventricular dysfunction and who are not dependent on right-to-left shunting of blood~~, wherein the source comprises a cylinder of compressed gas and/or a delivery device suitable to deliver nitric oxide gas for inhalation by a patient~~;

informing the medical provider that a recommended dose of inhaled nitric oxide gas for treatment of neonates with hypoxic respiratory failure is 20 ppm nitric oxide;

providing a first warning to the medical provider that inhaled nitric oxide is contraindicated in the treatment of neonates dependent on right-to-left shunting of blood; and

providing a second warning to the medical provider, distinct from the first warning, that in patients with pre-existing left ventricular dysfunction, inhaled nitric oxide may increase pulmonary capillary wedge pressure (PCWP), leading to pulmonary edema, the second warning being sufficient to cause a medical provider considering inhaled nitric oxide treatment for a plurality of neonatal patients who (a) are suffering from a condition for which inhaled nitric oxide is indicated, and (b) have pre-existing left ventricular dysfunction, to elect to avoid treating one or more of the plurality of patients with inhaled nitric oxide in order to avoid putting the one or more patients at risk of pulmonary edema.

2.-5. (Canceled)

6. (Currently amended) The method of claim 1, wherein the dose recommendation and the first and second warnings appear in prescribing information supplied to the medical provider with the cylinder containing compressed ~~source of~~ nitric oxide gas.

7. (Currently amended) The method of claim 1, further comprising:

performing at least one diagnostic process to identify a first neonate patient who has hypoxic respiratory failure and is a candidate for 20 ppm inhaled nitric oxide treatment, wherein the first neonate patient is not dependent on right to left shunting of blood;

determining that the first neonate patient has pre-existing left ventricular dysfunction;

evaluating the potential benefit of treating the first neonate patient with 20 ppm inhaled nitric oxide vs. the potential risk described in the second warning that inhaled nitric oxide could cause an increase in PCWP leading to pulmonary edema in patients who have pre-existing left ventricular dysfunction, in order to arrive at a decision of whether or not to treat the first neonate patient with inhaled nitric oxide;

identifying a second neonatal patient as having hypoxic respiratory failure, not being dependent on right to left shunting of blood, and not having left ventricular dysfunction; and

treating the second neonatal patient with 20 ppm inhaled nitric oxide.

8. (Currently amended) The method of claim 1, further comprising:

performing at least one diagnostic process to identify a plurality of neonate patients who have hypoxic respiratory failure and are candidates for inhaled nitric oxide treatment, wherein the patients of the plurality are not dependent on right to left shunting of blood;

determining prior to treatment with inhaled nitric oxide whether or not each patient of the plurality has pre-existing left ventricular dysfunction;

determining that a first patient of the plurality does not have pre-existing left ventricular dysfunction;

treating the first patient with 20 ppm inhaled nitric oxide;

determining that other patients of the plurality do have pre-existing left ventricular dysfunction; and

for each patient of the plurality determined to have pre-existing left ventricular dysfunction, evaluating on a case-by-case basis the potential benefit of treating the patient with 20 ppm inhaled nitric oxide vs. the potential risk described in the second warning that inhaled nitric oxide could cause an increase in PCWP, leading to pulmonary edema;

for at least one patient of the plurality determined to have pre-existing left ventricular dysfunction, determining that the potential benefit of the treatment outweighs the potential risk described in the second warning; and

treating the at least one patient with 20 ppm inhaled nitric oxide.

9. (Currently amended) The method of claim 7, wherein the dose recommendation and the first and second warnings appear in prescribing information supplied to the medical provider with the cylinder containing compressed ~~source of~~ nitric oxide gas.

10. (Currently amended) The method of claim 8, wherein the dose recommendation and the first and second warnings appear in prescribing information supplied to the medical provider with the cylinder containing compressed ~~source of~~ nitric oxide gas.

11.-20. (Canceled)

21. (Currently amended) A method of providing ~~distributing~~ a pharmaceutical product, the method comprising:

generating a cylinder containing compressed nitric oxide gas by a process comprising compressing nitric oxide and nitrogen gases under high pressure;

supplying the cylinder containing compressed ~~a source of~~ nitric oxide gas to a medical provider responsible for treating a plurality of neonates with hypoxic respiratory failure, including some who do not have pre-existing left ventricular dysfunction and who are not dependent on right-to-left shunting of blood~~, wherein the source comprises a cylinder of~~

~~compressed gas and/or a delivery device suitable to deliver nitric oxide gas for inhalation by a patient~~;

informing the medical provider that a recommended dose of inhaled nitric oxide gas for treatment of neonates with hypoxic respiratory failure is 20 ppm nitric oxide;

providing a first warning to the medical provider that inhaled nitric oxide is contraindicated in the treatment of neonates dependent on right-to-left shunting of blood;

providing a second warning to the medical provider, distinct from the first warning, stating that patients who have pre-existing left ventricular dysfunction and are treated with inhaled nitric oxide may experience pulmonary edema, and recommending that, if pulmonary edema occurs in a patient who has pre-existing left ventricular dysfunction and is treated with inhaled nitric oxide, the treatment with inhaled nitric oxide should be discontinued.

22.-24. (Canceled)

25. (Currently amended) The method of claim 21, wherein the dose recommendation and the first and second warnings appear in prescribing information supplied to the medical provider with the cylinder containing compressed ~~source of~~ nitric oxide gas.

26. (Currently amended) The method of claim 21, further comprising:

performing at least one diagnostic process to identify a neonatal patient who has hypoxic respiratory failure and is a candidate for inhaled nitric oxide treatment;

determining prior to treatment with inhaled nitric oxide that the neonatal patient is not dependent on right to left shunting of blood, but does have pre-existing left ventricular dysfunction consistent with a pulmonary capillary wedge pressure greater than or equal to 20 mm Hg;

treating the neonatal patient with 20 ppm inhaled nitric oxide, whereupon the patient experiences pulmonary edema; and

following the recommendation in the second warning, discontinuing the treatment with inhaled nitric oxide due to the patient's pulmonary edema.

27.-30. (Canceled)

31. (Previously presented) The method of claim 8, wherein the at least one patient is monitored for evidence of increased PCWP and/or for evidence of pulmonary edema during treatment with 20 ppm inhaled nitric oxide.

32. (Currently amended) The method of claim [[18]]26, wherein the ~~at least one~~ neonatal patient is monitored for evidence of increased PCWP and/or for evidence of pulmonary edema during treatment with 20 ppm inhaled nitric oxide.

33. (New) A method of providing a pharmaceutical product, the method comprising:

supplying a source of nitric oxide gas to a medical provider responsible for treating a plurality of neonates with hypoxic respiratory failure, including some who do not have left ventricular dysfunction and who are not dependent on right-to-left shunting of blood, wherein the source comprises a cylinder of compressed gas and/or a delivery device suitable to deliver nitric oxide gas for inhalation by a patient;

informing the medical provider that a recommended dose of inhaled nitric oxide gas for treatment of neonates with hypoxic respiratory failure is 20 ppm nitric oxide;

providing a first warning to the medical provider that inhaled nitric oxide is contraindicated in the treatment of neonates dependent on right-to-left shunting of blood; and

providing a second warning to the medical provider, distinct from the first warning, that in patients with pre-existing left ventricular dysfunction, inhaled nitric oxide may increase PCWP, leading to pulmonary edema, the second warning being sufficient to cause a medical provider considering inhaled nitric oxide treatment for a plurality of neonatal patients who (a) are suffering from a condition for which inhaled nitric oxide is indicated, and (b) have pre-existing left ventricular dysfunction, to elect to avoid treating one or more of the plurality of patients with inhaled nitric oxide in order to avoid putting the one or more patients at risk of pulmonary edema;

performing at least one diagnostic process to identify a first neonate patient who has hypoxic respiratory failure and is a candidate for 20 ppm inhaled nitric oxide treatment, wherein the first neonate patient is not dependent on right to left shunting of blood;

determining that the first neonate patient has pre-existing left ventricular dysfunction;

evaluating the potential benefit of treating the first neonate patient with 20 ppm inhaled nitric oxide vs. the potential risk described in the second warning that inhaled nitric oxide could cause an increase in PCWP leading to pulmonary edema in patients who have pre-existing left ventricular dysfunction, in order to arrive at a decision of whether or not to treat the first neonate patient with inhaled nitric oxide;

identifying a second neonatal patient as having hypoxic respiratory failure, not being dependent on right to left shunting of blood, and not having left ventricular dysfunction; and

treating the second neonatal patient with 20 ppm inhaled nitric oxide.

34. (New) The method of claim 33, wherein the dose recommendation and the first and second warnings appear in prescribing information supplied to the medical provider with the source of nitric oxide gas.

35. (New) A method of providing a pharmaceutical product, the method comprising:

supplying a source of nitric oxide gas to a medical provider responsible for treating a plurality of neonates with hypoxic respiratory failure, including some who do not have pre-existing left ventricular dysfunction and who are not dependent on right-to-left shunting of blood, wherein the source comprises a cylinder of compressed gas and/or a delivery device suitable to deliver nitric oxide gas for inhalation by a patient;

informing the medical provider that a recommended dose of inhaled nitric oxide gas for treatment of neonates with hypoxic respiratory failure is 20 ppm nitric oxide;

providing a first warning to the medical provider that inhaled nitric oxide is contraindicated in the treatment of neonates dependent on right-to-left shunting of blood; and

providing a second warning to the medical provider, distinct from the first warning, that in patients with pre-existing left ventricular dysfunction, inhaled nitric oxide may increase PCWP, leading to pulmonary edema, the second warning being sufficient to cause a medical provider considering inhaled nitric oxide treatment for a plurality of neonatal patients who (a) are suffering from a condition for which inhaled nitric oxide is indicated, and (b) have pre-existing left ventricular dysfunction, to elect to avoid treating one or more of the plurality of patients with inhaled nitric oxide in order to avoid putting the one or more patients at risk of pulmonary edema;

performing at least one diagnostic process to identify a plurality of neonate patients who have hypoxic respiratory failure and are candidates for inhaled nitric oxide treatment, wherein the patients of the plurality are not dependent on right to left shunting of blood;

determining prior to treatment with inhaled nitric oxide whether or not each patient of the plurality has pre-existing left ventricular dysfunction;

determining that a first patient of the plurality does not have pre-existing left ventricular dysfunction;

treating the first patient with 20 ppm inhaled nitric oxide;

determining that other patients of the plurality do have pre-existing left ventricular dysfunction; and

for each patient of the plurality determined to have pre-existing left ventricular dysfunction, evaluating on a case-by-case basis the potential benefit of treating the patient with 20 ppm inhaled nitric oxide vs. the potential risk described in the second warning that inhaled nitric oxide could cause an increase in PCWP, leading to pulmonary edema;

for at least one patient of the plurality determined to have pre-existing left ventricular dysfunction, determining that the potential benefit of the treatment outweighs the potential risk described in the second warning; and

treating the at least one patient with 20 ppm inhaled nitric oxide.

36. (New) The method of claim 1, wherein the dose recommendation and the first and second warnings appear in prescribing information supplied to the medical provider with the source of nitric oxide gas.

REMARKS

Upon entry of the above amendments, claims 1, 6-10, 21, 25, 26, and 31-36 will be pending, claims 3 and 5 having been previously canceled, claims 2, 4, 11-20, 22-24, and 27-30 newly canceled above, and claims 33-36 newly added. Support for the amendments to independent claims 1 and 21 can be found in original claims 4 and 24 (now canceled) and in the specification, e.g., at paragraphs [0005] and [0006]. The amendments to various dependent claims are intended to ensure the latter remain consistent with the claims from which they depend. New independent claim 33 is based on a combination of previously pending claims 1 and 7; new independent claim 35 is based on a combination of previously pending claims 1 and 8. New dependent claims 34 and 36 are based on previously pending claim 6. Applicant has also amended the specification to correct two inadvertent errors at paragraphs [0058] and [0064]. The INOT22 study had a total of 124 subjects, not 134 subjects. The correct number (124) is disclosed in paragraph [0067], which says "The overall rate [of SAEs] is 7/124 (5.6%)...," indicating that the total number of subjects in the study was 124. No new matter has been added.

Priority

The independent claims prior to the present amendment were drawn to "A method of distributing a pharmaceutical product." The Final Office Action dated April 17, 2013, states that, because the Examiner identified no disclosure of that phrase in any of the "parent documents," "Applicant is only afforded the filing date of the instant application which is 11/21/12." Applicant maintains that the disclosure present in each of the related applications to which this application claims priority (i.e., the applications listed in the Cross Reference to Related Applications at paragraph [0001] of the present specification) generally disclosed the concept of distributing a source of pharmaceutically acceptable nitric oxide gas, which is certainly a pharmaceutical product. However, to expedite prosecution, applicant has deleted the term "distributing" from the claims. The independent claims are now drawn to "A method of providing a pharmaceutical product," as supported, e.g., at paragraphs [0005] and [0006]. The Examiner is respectfully asked to acknowledge that all of the claims as presently amended are fully supported by all of the parental applications, and further that all of the claims are entitled to the priority date of the earliest priority application, i.e., June 30, 2009.

Rejection under 35 USC §101

Claims 1, 2, 6, 11-13, 15, 16, 21-23, 25, 27 and 28 were rejected as allegedly directed to non-statutory subject matter. Claims 2, 11-13, 15, 16, 22, 23, 27 and 28 are presently canceled, so the rejection is moot as to them. Applicant continues to disagree with this ground of rejection for the reasons stated in the Reply filed April 2, 2013. However, to move the case forward to allowance, applicant has amended the independent claims to incorporate the limitations of certain dependent claims (claims 4, 7, 8, and 24) that were not rejected on this ground. For example, amended independent claims 1 and 21 now include the limitations of claims 4 and 24, respectively. New independent claim 33 combines the limitations of original claim 1 and claim 7, while new independent claim 35 combines the limitations of original claim 1 and claim 8. The remaining claims all depend from one of these independent claims. Accordingly, withdrawal of the rejection is respectfully requested.

Rejection under 35 USC §103(a)

All of the pending claims were rejected as obvious over a 2008 Belgian marketing authorization for a nitric oxide gas product with the trade name "VasoKINOX", in view of Kazerooni et al. (Cardiopulmonary Imaging 2004, Lippincott Williams & Wilkins, pages 234 and 236 in part) and Loh et al. (Circulation 1994, 90, pages 2780-2785) and Leo (Primary Care Companion, J Clin Psychiatry 1999 1:5; pages 131-141) and Himashree et al. (Current Science 2003, 85, 5, pages 607-614) and McLaughlin et al. (Circulation 2006, 114, pages 1417-1431). Applicant traverses the rejection on at least two independent grounds, either of which would be sufficient to overcome the rejection:

1. The primary reference, referred to in the Final Office Action as "VasoKINOX", is not citable as prior art against the present claims.

2. The Examiner has misconstrued many of the teachings of the cited art in significant ways, has failed to take into account how a person of ordinary skill in the art at the filing date would have interpreted the teachings, and has established neither a motivation to carry out the

claimed methods nor a reasonable expectation of success upon doing so, so has not established a prima facie case of obviousness.

These two grounds are discussed in turn below.

1. The primary reference, referred to in the Final Office Action as "VasoKINOX", is not citable as prior art against the present claims.

The VasoKINOX marketing authorization ("VasoKINOX") bears a date of July 14, 2008, which is less than a year prior to the present application's June 30, 2009, priority date. It therefore does not qualify as prior art under 35 USC § 102(b). Applicant submits that it also does not qualify as prior art under 35 USC § 102(a), as evidenced by the Declaration under 37 C.F.R. § 1.131 attached as Exhibit A (the "Rule 131 Declaration") establishing that the inventor, Dr. James Baldassarre[1], conceived of the invention and reduced it to practice prior to July 14, 2008.

The Rule 131 Declaration provides evidence that, upon reviewing data regarding severe adverse events (SAEs) recorded during the course of the INOT22 clinical 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), Dr. Baldassarre recognized that the risk of pulmonary edema in pediatric patients inhaling nitric oxide gas was higher in patients with pre-existing left ventricular dysfunction than in those without pre-existing left ventricular dysfunction. This recognition was memorialized after completion of the INOT22 study in a draft Clinical Study Report that Dr. Baldassarre helped author and that is attached to the Rule 131 Declaration as Appendix 5.[2] See, ¶ 13 of the Rule 131 Declaration, which quotes from page 77 of the draft Clinical Study Report as follows:

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[1] Documents effecting a change in the named inventors from "James S. Baldassarre and Ralf Rosskamp" to "James S. Baldassarre" were filed on November 19, 2013.

[2] The Rule 131 Declaration notes at paragraph 6 that all dates on its Appendix 1-5 documents have been redacted, but are all prior to July 14, 2008.

> **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.**

Dr. Baldassarre further states in ¶ 13 that he realized at the time the draft Clinical Study Report was prepared that the increased risk of pulmonary edema applies not only to the categories of pediatric patients who were the subject of the INOT22 study, but also applies more generally—e.g., encompassing all pediatric patients who are being treated with inhaled nitric oxide and oxygen and happen to have pre-existing elevated PCWP or other signs of poor left ventricle function. Dr. Baldassarre notes:

> 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.

Dr. Baldassarre also observes in ¶ 13 that

> 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.

Given the facts recited in the Rule 131 Declaration, applicant submits that the draft Clinical Study Report constitutes an actual reduction to practice of the presently claimed invention prior to July 14, 2008.

Further, applicant reminds the Office that, when "swearing behind" a reference, the applicant is required to show no more than the reference shows. See, *In re Stryker*, 435 F.2d 1340 (CCPA 1971). In the present case, applicant has shown that Dr. Baldassarre discovered, prior to the July 14, 2008, date of VasoKINOX, the risk of using inhaled nitric oxide in pediatric patients with significantly elevated PCWP or other signs of poor left ventricle function. As discussed in detail below in part 2, VasoKINOX does not say that the LVD contraindication applies to pediatric patients, does not say that LVD increases the risk of pulmonary edema in patients given inhaled NO, and does not even say that the LVD contraindication is a safety-related contraindication, as opposed to an efficacy-related contraindication. Accordingly, the showing in the Rule 131 Declaration actually surpasses any "showing" in VasoKINOX insofar

as relevance to the present invention is concerned. Applicant submits that VasoKINOX does not qualify as prior art against the present claims. The Office has not even alleged that the rejection can stand without VasoKINOX, the primary reference cited in the obviousness rejections.

2. The Examiner has misconstrued many of the teachings of the cited art in significant ways, has failed to take into account how a person of ordinary skill in the art at the filing date would have interpreted the teachings, and has established neither a motivation to carry out the claimed methods nor a reasonable expectation of success upon doing so.

Several examples of the Final Office Action's problematic interpretations of the prior art's teachings (any one of which would warrant withdrawal of the rejection) are described below. When the teachings of the art are properly read, applicant's claims--whether before or after the present amendments--cannot be said to be obvious.

The VasoKINOX marketing authorization is described on page 7 of the Final Office Action as teaching methods of distributing the VasoKINOX product for use in treating "pulmonary hypertension," which the Final Office Action asserts is "a form of hypoxic respiratory failure." The Final Office Action points to three of the contraindications listed on page 25 and 32 of VasoKINOX (the three contraindications being left ventricular dysfunction (LVD), all forms of pulmonary arterial hypertension due to pulmonary hyper-flow, and newborns dependent on a right-to-left shunt), and also says that "VasoKINOX warns of pulmonary edema" on pages 27 and 35. Based on these alleged teachings in VasoKINOX, the Final Office Action draws the following conclusions:

> Consequently, it is implicit in the disclosure of [VasoKINOX] for the medical provider to evaluate/make the decision…to exclude any number of newborns who meet the exclusion criteria and thus avoid the risk of putting one or more of these patients at risk of pulmonary edema and administer [VasoKINOX] to any number of patients including newborns who pass the exclusion criteria….In other words, if the newborn is not dependent on right to left shunting of blood and does not have LVD then the medical provider makes the decision to treat the newborn with 20 ppm inhaled NO. Final Office Action at pages 8-9.

Applicant submits that some of the Office's assumptions underlying the above characterization of VasoKINOX are not accurate, and so the Office's summary of what is "implicit" in that reference does not reflect how one of ordinary skill in the art would read the reference.

First, pulmonary hypertension is *not* "a form of hypoxic respiratory failure," as alleged by the Office, and the VasoKINOX reference does not say it is. See ¶¶ 8-9 of the Declaration of Douglas A. Greene, M.D., under 37 C.F.R. § 1.132, enclosed as Exhibit B ("Greene Declaration"). This point is important because the condition specified in applicant's claims is "neonates with hypoxic respiratory failure," a condition that is not even mentioned in VasoKINOX. Pulmonary hypertension refers to a condition in which the hydrostatic pressure of the blood within the pulmonary blood vessels is increased. This condition can have many very different proximal causes and can be associated with many very different categories of conditions. See, e.g., the various World Health Organization categories of pulmonary hypertension and associated conditions listed in Table 1 on page 1419 of McLaughlin et al. In contrast, hypoxic respiratory failure refers to any condition in which disease of the airways or the blood vessels of the lung impairs gas exchange leading to under-oxygenation of the blood.[3] Pulmonary hypertension in the context of some of the conditions listed in Table 1 of McLaughlin et al. (e.g., persistent pulmonary hypertension of the newborn, or PPHN) can lead to hypoxic respiratory failure, but pulmonary hypertension in the context of many of the other listed conditions would not. Thus, while the two different conditions can sometimes coexist in the same patient (as in PPHN), one certainly cannot say that either condition is a "form of" the other.[4]

VasoKINOX teaches use of inhaled nitric oxide in just one particular setting: to treat *perioperative and postoperative pulmonary hypertension in the context of cardiac surgery*. See, section 4.1 of VasoKINOX. As explained on page III-172 of McMullan et al., Circulation 102[suppl III]:III-172-III-178 (2000) (included in the Information Disclosure Statement filed with this Reply), pulmonary hypertension is a frequent side effect of the cardiac bypass procedure commonly employed during heart surgery. Pulmonary hypertension in this setting is thought to be caused, at least in part, by a temporary decrease in endogenous nitric oxide that normally is produced naturally in the patient's pulmonary arteries. When the patient's blood is directed through a cardiac bypass machine instead of through the heart and lungs during cardiac surgery, the blood vessels of the lungs lose some of their ability to generate endogenous nitric

[3] Greene Declaration at ¶ 9.
[4] *Id.*

oxide. The resulting decrease in endogenous nitric oxide may contribute to a tendency of the pulmonary blood vessels to constrict when blood flow through the vessels is re-established at the end of the surgery. The result is *perioperative and postoperative pulmonary hypertension*—the condition described in VasoKINOX. Pulmonary hypertension in this situation puts the patient at risk *not* of hypoxia or hypoxic respiratory failure, but rather of an overworked and overloaded right ventricle that has to pump at unduly high pressure against the constricted pulmonary arteries.[5] Inhaling nitric oxide gas during and after the surgery supplies exogenous nitric oxide to the pulmonary vessels, opening them up so that the patient's right ventricle can work efficiently and without undue stress to pump blood through the lungs after removal of the cardiopulmonary bypass.[6]

VasoKINOX's use of inhaled nitric oxide to treat *perioperative and postoperative pulmonary hypertension in the context of cardiac surgery* has nothing whatsoever to do with treatment of *hypoxic respiratory failure in neonates*, the condition recited in the present claims. Neither of these conditions is a "form" of the other: rather, they are entirely different conditions, albeit both involving an aspect of pulmonary hypertension. *Perioperative and postoperative pulmonary hypertension in the context of cardiac surgery* is described above. *Hypoxic respiratory failure in neonates* typically occurs due to an abnormal persistence of the fetal cardiopulmonary physiology after birth. Prior to birth, the fetus' blood is shunted from the right side of the heart directly to the left side and/or to the systemic circulation, rather than into the lungs, which are normally vasoconstricted until birth. At birth, the fetal shunts in the heart are supposed to close, permitting the right side of the heart to pump blood into the lungs instead of through the shunts, and the pulmonary vessels are supposed to relax so that the blood can flow relatively unimpeded through the lungs. When the fetal cardiopulmonary physiology persists after birth, normal blood flow through the lungs does not happen as it is supposed to. This means the blood does not get sufficiently oxygenated, resulting in hypoxic respiratory failure and a "blue baby." Administering inhaled nitric oxide can alleviate the hypoxic respiratory failure in such neonates by opening up the pulmonary blood vessels and thereby increasing blood flow

[5] Greene Declaration at ¶ 10.
[6] *Id.*

from the right heart into the lungs. This decreases blood flow through the shunts and improves oxygenation.[7]

Thus, it is not medically accurate to refer to pulmonary hypertension in general, and particularly the narrow subset of pulmonary hypertension described in VasoKINOX (*perioperative and postoperative pulmonary hypertension in the context of cardiac surgery*), as being a "form of hypoxic respiratory failure." VasoKINOX did not teach treatment of hypoxic respiratory failure, nor of any subset or "form" of hypoxic respiratory failure.

Second, the conclusions drawn by the Final Office Action based on VasoKINOX's bare listing of "left ventricular dysfunction" as a contraindication appear to be based more on hindsight than on what the reference actually says. VasoKINOX provides no explanation of why, or in what situations, LVD would be contraindicated. Applicant will therefore examine some possible theoretical ways the VasoKINOX contraindication might be interpreted, to help elucidate which if any interpretations would have made sense before the present application's priority date to a physician of ordinary skill in the art tasked with deciding whether to administer or withhold lifesaving treatment with inhaled nitric oxide to a patient who had LVD.

The broadest theoretically possible reading of the contraindication is that VasoKINOX is contraindicated in *all* LVD patients, without exception. As explained below, this broadest reading is plainly contrary to the available evidence, so is unlikely to be how one of ordinary skill in the art would have read the contraindication.

Inhaled nitric oxide was and is routinely used in the context of cardiac surgery (indeed, that is the sole approved indication taught by VasoKINOX), *including where the cardiac surgery is carried out to repair a dysfunctional left ventricle.* See, e.g., the discussion of successful use of inhaled nitric oxide in patients who have undergone surgery to receive a left ventricular assist device (which presumes they had LVD prior to surgery) at page 632 of Hayward et al., *Cardiovascular Research* (1999) 43:628-638; enclosed with the Information Disclosure Statement filed with this Reply. Such use of inhaled nitric oxide in LVD patients undergoing cardiac surgery was therefore well established before VasoKINOX was published; it remains commonplace today. VasoKINOX does not provide any data or rationale that one of skill in the art could interpret as a reason why this medically important use in LVD patients should cease. It

[7] *Id.* ¶ 11.

is clear that those of skill in the art did not at the priority date, and still do not, read the VasoKINOX contraindication as a general warning that inhaled nitric oxide should be avoided in *all* patients who have LVD, or even all cardiac surgery patients who have LVD.

Given that the broadest reading of the contraindication is presumably not the one that those of skill in the art would have selected, the question then is which of several theoretically possible narrower readings of the LVD contraindication might have been considered more appropriate by those of skill in the art. One possibility is an interpretation of the contraindication as applying solely to ***adult*** LVD patients, and not neonates or other pediatric patients. This interpretation has some support derived from teachings in the art (e.g., in Loh et al.) about the risk of administering inhaled nitric oxide to adult LVD patients. Adult LVD patients typically have a form of LVD resulting from heart attack or hypertensive disease, and characterized by a stiff left ventricle that cannot readily stretch to accommodate a sudden increase in blood flow, such as can be triggered by inhaling nitric oxide.[8] In Loh et al., a group of adult heart failure patients with pre-existing LVD from idiopathic or ischemic dilated cardiomyopathy were given inhaled nitric oxide as a way to reduce their elevated pulmonary vascular resistance (PVR). The authors report that inhaled nitric oxide caused not only a drop in PVR but also corresponding increases in left ventricular filling pressure and pulmonary artery wedge pressure in these patients (page 2782, left column). Based on these observations, Loh et al. conclude at page 2784, right column, that inhaled nitric oxide "may have adverse effects in such patients." *This conclusion in Loh et al. pertains solely to the type of patient studied in Loh et al.*, i.e., adult patients with a form of pre-existing LVD that renders the left ventricle stiff and non-compliant, and so unable to accommodate a sudden increase in blood volume. One of skill in the art would realize that there is no reason to assume Loh et al.'s conclusion also applies to neonatal LVD patients (such as those that are the subject of the presently claimed methods), whose LVD is typically of a very different type than that in Loh et al.'s adult patients. The type of LVD normally seen in pediatric patients is attributable not to a *stiff, non-compliant* left ventricle, but rather the opposite: a soft, overly elastic left ventricle.[9] As explained by Dr. Greene, the expectation in the art was that a soft, overly elastic left ventricle would be able to handle the

[8] Greene Declaration, ¶ 12-13.
[9] *Id.* ¶ 12.

sudden increase in blood volume by simply expanding, with no particular risk of an increase in pulmonary artery wedge pressure. Dr. Greene says that one cannot reasonably predict the hemodynamic response of a child or neonate with LVD and pulmonary hypertension based on knowledge of how Loh et al.'s adult patients responded to inhaled nitric oxide.[10]

That those of skill in the art did not expect that inhaled nitric oxide should be contraindicated in pediatric LVD, and so would not have read the LVD contraindication in VasoKINOX as applying to any patients other than adults with stiff, noncompliant left ventricles, is evidenced by a number of objective facts, including:

(1) The fact that FDA did not require such a contraindication or warning in the prescribing information for INOmax® nitric oxide gas for inhalation, a product approved for use solely in neonates, until *after* applicant informed FDA of the risk in pediatric patients, which happened *after* the present inventors' discovery of the risk when analyzing the results of a clinical trial (the INOT22 study) testing a new use for INOmax® in pediatric patients. Declaration of James S. Baldassarre, M.D., under 37 C.F.R. § 1.132, attached as Exhibit C ("Baldassarre 132 Declaration") at paragraphs 4-6, 16, and 17. Compare the INOmax prescribing information dated 2007 attached as Exhibit D, which does not identify LVD as a risk, to the revised INOmax prescribing information approved by FDA on August 28, 2009 (attached as Exhibit E), which states under "Warnings and Precautions" on page 1, right column: "In patients with pre-existing left ventricular dysfunction, inhaled nitric oxide may increase pulmonary capillary wedge pressure leading to pulmonary edema." This suggests that those of skill in the art at FDA were not aware of the risk in neonates until applicant pointed it out to them.

(2) The fact that the original study design for the INOT22 study, which was initiated in 2004, did not exclude patients with LVD.[11] This illustrates that the experts in pediatric cardiology who designed the study, as well as the many experts that reviewed the study design before it was approved, did not realize that inhaled nitric oxide posed any sort of risk in pediatric patients with LVD. Not a single one of the over 100 experts involved in

[10] *Id.* ¶ 13.
[11] Baldassarre 132 Declaration, ¶¶ 6, 10.

the design and approval of the INOT22 study raised a question about whether pediatric LVD patients should be excluded from the trial.[12] If any of these experts was aware of a possible risk to such patients, he or she certainly would have raised the question.

Yet another theoretically possible interpretation of the LVD contraindication in VasoKINOX is that the contraindication applies solely to patients who happen to emerge from their cardiac surgery with a left ventricle that, due to the traumatic effects of the surgery, cannot stretch normally. This interpretation takes into account several facts: (a) VasoKINOX teaches use of inhaled nitric oxide *solely in the context of cardiac surgery*; (b) the art is aware (e.g., from Loh et al.) that a stiff left ventricle may not be able to accommodate the increased volume of blood resulting from inhaled nitric oxide; and (c) the VasoKINOX contraindication (unlike the LVD warning now included in the INOmax prescribing information, and unlike the warning required by the present claims) does not specify "*pre-existing*" LVD, so applies to LVD that arises during or immediately after the cardiac surgery. One of skill in the art who was aware of Loh et al.'s teachings could reasonably read the LVD contraindication in VasoKINOX as limited to a cardiac surgery patient who emerges from the surgery with a dysfunctional left ventricle that is stiff and unable to expand sufficiently to handle the expected increased volume of blood, and so who (like Loh et al.'s patients) is at risk of a dangerously increased pulmonary arterial wedge pressure as a result of treatment with inhaled nitric oxide. Such a patient might have been suffering from a stiff left ventricle even before the surgery, or might have undergone trauma during the surgery that at least temporarily reduces the ability of the left ventricle to expand normally to accommodate the increased volume of blood. There is no teaching in Loh et al. or VasoKINOX or any other cited art that the same risk applies to LVD patients (such as neonates) whose left ventricles are soft and overly compliant, so presumably remain capable of expanding to accommodate an increased volume of blood. Nor is there any compelling reason to read the LVD contraindication as applying to patients outside the cardiac surgery context, given that VasoKINOX is solely about use of inhaled nitric oxide during and after cardiac surgery.

[12] *Id.* ¶¶ 7-14.

A final plausible interpretation of the unexplained LVD contraindication in VasoKINOX is one based on expected *lack of efficacy*, rather than on a safety risk.[13] It is known in the art that LVD itself can actually *cause* pulmonary hypertension. See, e.g., McLaughlin et al. at page 1421, left column, which discusses pulmonary hypertension caused by back pressure in the context of left heart disease. According to McLaughlin et al., the "primary approach" to reducing the pulmonary hypertension in this situation is ameliorating the underlying cause, i.e., the LVD. McLaughlin et al. does not suggest using inhaled nitric oxide; according to Dr. Greene, this is probably because this form of pulmonary hypertension does not involve pulmonary vasoconstriction, *so cannot be alleviated by inhaling nitric oxide*.[14] Accordingly, one of skill in the art might very well interpret the LVD contraindication in VasoKINOX as meaning that inhaled nitric oxide should not be administered in cases where the patient's pulmonary hypertension is *caused by* his or her LVD, for the simple reason that the treatment will not be at all effective in alleviating the pulmonary hypertension. It would be pointless to subject such a patient to a treatment that has no possibility of being helpful.

In short, there are a number of theoretically possible ways that one of ordinary skill in the art might have read the LVD contraindication. The broadest one (encompassing *all* LVD patients) is contrary to the evidence, so is unlikely to be the correct one. The other possibilities described above do not encompass the patients who are the subject of the presently claimed methods: **neonates who have pre-existing LVD and are candidates for inhaled nitric oxide due to hypoxic respiratory failure**. Accordingly, one simply can't assume, as the Office has done, that the contraindication means it was known in the art to exclude neonates who have pre-existing LVD and hypoxic respiratory failure (a condition not mentioned in VasoKINOX) from treatment with inhaled nitric oxide. In fact, one can't assume that the contraindication applies to neonates at all—even those undergoing cardiac surgery—given the important differences

[13] A treatment can be "contraindicated" in a given condition based on expected *lack of efficacy*, and need not involve an expected risk of harm. Greene Declaration, ¶ 14. For example, the VasoKINOX contraindication for "all forms of pulmonary arterial hypertension due to pulmonary hyper-flow" is likely based upon a realization in the art that inhaled nitric oxide would be *ineffective* at reducing pulmonary arterial hypertension that is attributable to pulmonary hyper-flow (high pressure from the right side of the heart or from a systemic-to-pulmonary shunt causing abnormally high blood flow through the lungs, which in turn causes pulmonary arterial hypertension). See, e.g., McLaughlin et al., page 1420, last paragraph.

[14] Greene Declaration, ¶ 14.

between adult LVD and neonatal LVD. Though the approved indication in VasoKINOX includes both adults and children (including neonates), that does not mean that all of the contraindications apply to all age groups. Furthermore, there is no reason to assume, as the Office has done, that the LVD contraindication is about a risk of harm, as opposed to lack of efficacy in patients whose pulmonary hypertension is *caused by* their LVD (a situation entirely unrelated to hypoxic respiratory failure). Absent a logical reason to read the LVD contraindication as applying to neonates with hypoxic respiratory failure--a reason found nowhere in VasoKINOX or the other cited art--one of skill in the art prior to the present invention would not have denied neonates with hypoxic respiratory failure a lifesaving treatment simply because they have LVD.

Third, VasoKINOX does not suggest there is any link between the contraindication for LVD and the "cases of pulmonary edema" mentioned on pages 27 and 35 of the reference. The Office apparently assumes there is a link, as evidenced by the statement from the Final Office Action quoted above about excluding newborns "who meet the exclusion criteria[15] and thus avoid the risk of putting one or more of these patients at risk of pulmonary edema." However, a careful examination of VasoKINOX shows that the putative link implied by that statement from the Final Office Action does not exist. VasoKINOX explicitly attributes the "cases of pulmonary edema" to "administration of high concentrations of inhaled nitric oxide," and not to the presence of LVD (see, VasoKINOX at pages 27 and 35). Those of skill in the art are well aware that a high concentration (e.g., 5000 to 20,000 ppm) of inhaled nitric oxide can cause severe pulmonary edema and death. See, e.g., Himashree et al., page 611, last paragraph. A case of accidental inhalation of a very high concentration of nitric oxide that produced severe pulmonary edema in a patient was reported in 1967 (Clutton-Brock, Brit. J. Anaesth. 39:388-392 (1967); cited in the Information Disclosure Statement filed with this Reply). Other articles published in the same issue of that journal reported that subsequent experiments in animals confirmed this effect (see, e.g., Shiel, Brit. J. Anaesth. 39:413 (1967); cited in the Information Disclosure Statement filed with this Reply). Clutton-Brock describes a patient who had been given the anesthetic gas nitrous oxide ("laughing gas") in preparation for an operation; the patient became very ill after inhaling the gas and died less than 24 hours later. The results of

[15] "Exclusion criteria" is an apparent reference to the contraindications in VasoKINOX.

postmortem examination showed that "her lungs were extremely oedematous" (page 390, last paragraph), i.e., she had severe pulmonary edema at death. Before the cause of the problem was discovered, a second patient was given anesthetic from the same tank of nitrous oxide and also became very ill. Analysis of the canister of nitrous oxide later revealed that it was highly contaminated with nitric oxide (page 390, last paragraph)—"apparently in excess of 1.5 per cent" (page 392, right column, first full paragraph), which means that the canister contained over 15,000 ppm nitric oxide. The anesthetic gas was administered as 75% of the inhaled gas (the other 25% being oxygen); accordingly, the first patient received a dose of at least 11,250 ppm nitric oxide for at least 25 minutes (page 388, left column, to page 389, left column). There is no suggestion in Clutton-Brock that the first patient had underlying pulmonary hypertension or LVD prior to inhalation of the contaminated nitrous oxide. Indeed, the author reports that the patient was "very healthy", and about to undergo a hysterectomy (page 388, left column, second paragraph). Thus, the pulmonary edema she experienced was presumably due to physical damage to lung tissues caused by the extremely high level of nitric oxide (a potent oxidizing agent), [16] and not due to the hemodynamic effects of inhaled nitric oxide in adult patients who have both pulmonary hypertension and LVD.

In the same issue of the British Journal of Anaesthesiology, the Shiel article describes experiments in healthy dogs that were undertaken in response to the tragic accidental poisoning described in Clutton-Brock. Dogs who inhaled 2% or 0.5% nitric oxide (i.e., 20,000 ppm or 5,000 ppm nitric oxide) in oxygen for periods ranging from 7-50 minutes all developed "intra-alveolar oedema" (see, Table 1 on page 415 and page 419, right column, section (A)) and died. Again, this toxic effect of high levels of nitric oxide has nothing to do with pre-existing pulmonary hypertension and/or LVD. It has nothing to do with increased blood flow caused by inhaled nitric oxide, nor overloading a left ventricle that can't handle the blood flow. Applicant submits that Clutton-Brock, Shiel, and other similar reports are likely to be the source of the remark in VasoKINOX that "cases of pulmonary edema have been reported after administration of high concentrations of inhaled nitric oxide." This conclusion is supported by the remark in

[16] It is also possible that the lung injury was caused in part by nitrogen dioxide that either was present as an original contaminant along with nitric oxide in the cylinder of nitrous oxide, or was a product of the reaction of nitric oxide with oxygen in the inhaled gas mixture. Since the rate of conversion of nitric oxide to nitrogen dioxide in the presence of oxygen is proportional to the square of the concentration of nitric oxide, the higher the concentration of nitric oxide, the more rapid the conversion to nitrogen dioxide.

Himashree et al. about pulmonary edema following inhalation of 5000 to 20,000 ppm nitric oxide. The Office has not cited a single report of a case in which pulmonary edema resulted from administration of a "high concentration" of inhaled nitric oxide to a subject who had pulmonary hypertension and pre-existing LVD that might support the Office's apparent assumption that the LVD contraindication in VasoKINOX is linked to a risk of pulmonary edema, or would be read that way by one of ordinary skill in the art. VasoKINOX does not even hint that the LVD contraindication has anything to do with pulmonary edema. Without that link, one simply cannot infer that VasoKINOX listed LVD as a contraindication specifically because of a perceived risk that inhaled nitric oxide can cause pulmonary edema in LVD patients. It is even more of a stretch to infer that the putative risk of pulmonary edema in LVD patients applies to the type of LVD seen in neonates (i.e., soft, overly-compliant left ventricles). In fact, one can't even infer that the LVD contraindication is due to a perceived safety risk at all, as it could just as reasonably be a warning that inhaled nitric oxide will not be *effective* in patients whose pulmonary hypertension is *caused by* their LVD. Furthermore, one cannot infer that the contraindication has relevance to any patients other than the cardiac surgery patients who are the subject of the approved indication. The patients encompassed by the present claims have *hypoxic respiratory failure*, a condition dramatically different from *perioperative or postoperative pulmonary hypertension in the context of cardiac surgery*.

Kazerooni et al. is cited for its general teachings about PCWP and left ventricular function (not ***dys***function, as stated in the Final Office Action), including the link between elevated PCWP and pulmonary edema.

Loh et al. is cited for its teachings that inhalation of nitric oxide in patients with LVD can increase PCWP. This reference is discussed above, in the context of the VasoKINOX discussion. A crucial fact not mentioned in the Final Office Action is that Loh et al.'s teachings are solely about a group of *adult* patients (mean age 52 years), whose LVD is from idiopathic or ischemic dilated cardiomyopathy. Such patients characteristically have a stiff, noncompliant left ventricle that cannot stretch sufficiently to accommodate a sudden increase in blood volume,

such as can occur when pulmonary vasoconstriction is relieved with inhaled nitric oxide.[17] The result can be a pressure backup from the left ventricle, producing increased PCWP. In contrast to the adult patients of Loh et al., the patients who are the subject of the presently claimed methods are all neonates. Neonatal LVD is typically fundamentally different than the sort of LVD found in Loh et al.'s adult patients. The Final Office Action fails to take into account the highly relevant physiological and functional differences between the type of LVD exhibited by the adult patients studied by Loh et al. and the type of LVD typically seen in neonates. These distinct differences, and their relevance to the question of obviousness of the presently claimed methods, are discussed above, so will not be repeated here.

Himashree et al. is a review article about high altitude pulmonary edema (HAPE), a form of pulmonary edema triggered when a subject spends time at a high altitude. Himashree et al. has nothing to do with LVD, and if anything *teaches away* from the presently claimed methods. According to Himashree et al., the pulmonary hypertension often associated with HAPE can be treated with inhaled nitric oxide. By teaching that inhaled nitric oxide can be safely given to patients who have pre-existing high altitude pulmonary edema, this reference effectively undermines any attempt to broadly connect use of inhaled nitric oxide with worsening (much less *causing*) pulmonary edema. The general understanding in the art was that the pulmonary edema risk posed by inhaled nitric oxide does was limited to a very narrowly defined set of patients: adults with the type of LVD typical of adults, involving a stiff, noncompliant left ventricle—such as taught by Loh et al. The Office has cited no evidence that such risk was expected in the art for any other categories of patients, including Himashree et al's HAPE patients as well as the only category relevant to the present claims, i.e., neonates with pre-existing LVD.

The Final Office Action cites Himashree et al. for its teachings that adverse effects of inhaled NO include systemic hypotension (probably a reference to the systemic hypotension that can arise when a neonate who is dependent on right-to-left shunting of blood is given inhaled nitric oxide—a well-known risk of this treatment). In addition, Himashree et al. is quoted in the Final Office Action as saying that infants "who receive INO therapy should be monitored according to protocols designed to avoid the potential toxic effects associated with INO administration." What the Final Office Action fails to note is that, though Himashree et al.

[17] Greene Declaration, ¶¶ 12-13.

describes several potential toxic effects of the gas in infants (see the sections of Himashree et al. cited in the Final Office Action), *pulmonary edema is not one of them*. This supports applicant's position that the art was not aware there was a risk that inhaled nitric oxide might cause pulmonary edema in infants, at least when administered at a concentration well below the extreme levels (e.g., 5000 to 20,000 ppm) shown to be lethal. See, e.g., Himashree et al. at page 611, last paragraph, which notes that such lethally high doses can cause pulmonary edema, also says that "there is little evidence of such toxicity when the concentration is kept in the normal range (1 to 30 ppm)." **Thus, Himashree et al. *teaches away* from a method that requires warning about a risk of pulmonary edema in neonates treated with 20 ppm inhaled nitric oxide.**

Leo is cited as allegedly teaching "that primary care physicians can make treatment decisions based on assessment of benefits and risks as shown in Table 1." Applicant points out that this mischaracterizes the teachings of this reference. Leo is concerned with how a physician should go about deciding whether a given *patient* has the mental capacity to make treatment decisions him/herself. See, e.g., the title and abstract of Leo. This reference says nothing about inhaled nitric oxide, LVD, pulmonary edema, hypoxic respiratory failure, or neonates, so is essentially irrelevant to the claims.

McLaughlin et al. is cited as allegedly teaching that echocardiography can be used to determine left heart disease and pulmonary arterial hypertension (PAH), and also that edema is a symptom of PAH. Regarding the latter teaching, the Final Office Action points to Table 2 on page 1420, which lists several "symptoms of PAH", including "edema." In the context of Table 2, it is apparent that "edema" refers not to *pulmonary* edema, but rather to *peripheral* edema (swelling of the lower extremities), which is a known symptom of PAH. See, e.g., page 194 of Chapter 14 of Principles of Pulmonary Medicine, Weinberger et al., ed., Elsevier Saunders, 2014 (attached as Exhibit F),[18] which lists (in the left margin) a number of physical signs of pulmonary hypertension including "peripheral edema" and says at the end of the second

[18] A copy of the entire Chapter 14 is included in the Information Disclosure Statement filed with this Reply, in case the Examiner wishes to read the entire chapter.

paragraph, "At this stage, both lower extremity peripheral edema and ascites may develop." The mention of "edema" in Table 2 of McLaughlin et al. therefore appears to refer to a type of edema that is *not* pulmonary edema--and so is irrelevant to the present claims. Furthermore, it is unclear what point the Office was trying to make in citing this mention of edema in McLaughlin et al. Reversing PAH with inhaled nitric oxide would presumably *alleviate* the symptoms of PAH (including edema, if that happens to be among the patient's symptoms), rather than increase the risk that they will occur. Thus, if McLaughlin et al.'s reference to "edema" as being a symptom of PAH actually did mean *pulmonary* edema, the reference would *teach away* from the presently claimed methods. Clarification of what was intended by the citation of McLaughlin et al.'s Table 2 is respectfully requested.

Page 11 of the Final Office Action describes, in three numbered paragraphs, the Office's view of the differences between the present application[19] and VasoKINOX. In the first numbered paragraph, "the difference" between the "application" and VasoKINOX is said to be that VasoKINOX does not expressly teach that inhaled NO may/could increase PCWP leading to a potential risk of pulmonary edema. This "deficiency" is said to be cured by the teachings of Kazerooni et al. and Loh et al.

Applicant points out that there are several "deficiencies" in VasoKINOX that are not addressed in that page 11 paragraph—deficiencies that are not cured by any of the cited prior art. In addition to the deficiency acknowledged by the Office, VasoKINOX fails to teach at least the following significant aspects of the method of claim 1:

- **Informing the medical provider that inhaled nitric oxide can be used to treat neonates with hypoxic respiratory failure.**

As explained above, pulmonary hypertension in the context of cardiac surgery (the sole indication taught by VasoKINOX) is not a "form of hypoxic respiratory failure," as presumed by the Office. VasoKINOX does not teach treating hypoxic respiratory failure, nor any "form"

[19] Applicant assumes that, by "application," the Examiner means "claims" (or even a particular claim, such as claim 1), since obviousness hinges on what the individual claims say, and not what an "application" says.

thereof, whether in neonates or any other patient. Thus, this limitation is not met by VasoKINOX.

- **Informing the medical provider that the recommended dose for treating neonates with hypoxic respiratory failure is 20 ppm.**

Since VasoKINOX does not teach treating hypoxic respiratory failure, it follows that the reference also does not teach a recommended dose for treating that condition in neonates.

- **Providing a warning to the medical provider that is sufficient to cause a medical provider considering inhaled nitric oxide treatment for neonatal patients who have pre-existing LVD to elect to avoid treating one or more of those patients with inhaled nitric oxide in order to avoid putting them at risk of pulmonary edema.**

The LVD contraindication in VasoKINOX does not specify that the LVD is "pre-existing," as required by the claim. As explained above, those of skill in the art at the time that VasoKINOX was published, and to this day, understand that inhaled nitric oxide is routinely and successfully used in patients who are undergoing cardiac surgery, where the surgery is intended to address their pre-existing LVD. Thus, it is unlikely that one of ordinary skill in the art would read the contraindication in VasoKINOX as applying to pre-existing LVD—i.e., LVD that existed prior to the cardiac surgery. This evidence also establishes that the contraindication in VasoKINOX does not satisfy the claim criterion requiring that the warning be "sufficient to cause a medical provider considering inhaled nitric oxide treatment for neonatal patients who have pre-existing LVD to elect to avoid treating one or more of those patients with inhaled nitric oxide." As discussed in detail above, either of the following interpretations of the contraindication in VasoKINOX would be more rational than the interpretation proposed by the Final Office Action:

(1) The contraindication applies not to patients with pre-existing LVD, but rather to patients who emerge from their cardiac surgery with left ventricles that are dysfunctional in the sense that they are, at least temporarily, unable to stretch normally to accommodate the rush of blood upon treatment with inhaled nitric oxide. That is neither pre-existing LVD nor the sort of LVD seen in neonates with hypoxic respiratory failure, so is irrelevant to the presently claimed methods.

(2) The contraindication is simply a warning that inhaled nitric oxide will not be efficacious in patients whose pulmonary hypertension is *caused by* their LVD. Though this condition (pulmonary hypertension *caused by* LVD) does involve what could be termed "pre-existing" LVD, the rest of the limitations of claim 1 would not be met for many reasons, e.g., (a) the condition is not one for which inhaled nitric oxide treatment is indicated (because it won't help); and (b) the reason inhaled nitric oxide would be avoided in patients with this condition has to do with expected lack of efficacy, rather than a concern about inducing pulmonary edema.

In sum, one of ordinary skill in the art would not reasonably interpret the VasoKINOX contraindication as corresponding to the warning described in claim 1.

Furthermore, applicant disagrees that *any* deficiency of VasoKINOX (even the one identified in the Final Office Action) is "cured" by the teachings of Kazerooni et al. and Loh et al. Neither of these references teaches that there might be a risk of increased PCWP or pulmonary edema in *neonates* with LVD who are treated with inhaled nitric oxide. As explained above, there is a distinct, and highly pertinent, difference between the "stiff, noncompliant" type of LVD seen in Loh et al.'s adult patients and the "soft, overly-compliant" type of LVD typically seen in neonates. While it is logical to expect that a stiff, noncompliant left ventricle would be unable to handle the increased volume of blood resulting from inhaled nitric oxide treatment, and so PCWP would rise and pulmonary edema result following the treatment, applicant's evidence of record establishes that it was considered very surprising that the soft, overly-compliant left ventricles typical of pediatric LVD patients would react similarly. Since neither Kazerooni et al. nor Loh et al. supplies the teaching linking pulmonary edema to *neonatal* LVD that is missing from VasoKINOX and that is unexpected in view of all of the references, those two references cannot be said to "cure" the many deficiencies of VasoKINOX.

Numbered paragraphs 2 and 3 on page 11 of the Final Office Action describe other differences between the application/claims and the teachings of VasoKINOX:

> …VasoKINOX [does] not expressly teach determining if the potential benefit of the treatment outweighs the potential risk described in the second warning and treating the patient with LVD with 20 ppm iNO or discontinuing treatment with iNO if pulmonary

> edema occurs. …VasoKINOX [does] not expressly teach performing echocardiography to identify a neonate who is a candidate for iNO treatment and discontinuing treatment due to hypotension or monitoring for evidence of an increase in PCWP or pulmonary edema during treatment.

According to the Final Office Action, these various deficiencies in VasoKINOX are cured by the teachings of Kazerooni et al., Loh et al. and Leo, and/or in further view of Himashree et al. and McLaughlin et al. Applicant can find no teaching anywhere in any of the cited references, even in combination, regarding determining whether the potential benefit of using inhaled nitric oxide to treat a neonate who has hypoxic respiratory failure and LVD outweighs the potential risk that inhaled nitric oxide could cause an increase in PCWP leading to pulmonary edema, so do not see how one could conclude that this deficiency is "cured" by the secondary references. Likewise, none of the cited references, even in combination, suggests discontinuing a treatment if pulmonary edema or hypotension occurs, or monitoring for evidence of an increase in PCWP or pulmonary edema during treatment. If the Examiner is aware of such teachings in the cited references, he is asked to point them out explicitly by page and paragraph or line so that applicant can address them.

Beyond the deficiencies identified by the Office, none of these references says anything about using inhaled nitric oxide to treat hypoxic respiratory failure in neonates (or in anyone else, for that matter). None of these references says anything about the type of pre-existing LVD typical in neonates, which is entirely different from LVD in adults (the concern of Loh et al.). None of these references suggests that there might be a risk of any sort (much less a risk of pulmonary edema in particular) in neonates who have pre-existing LVD and are treated with inhaled nitric oxide. None says that a medical provider should determine whether a potential benefit of treatment outweighs a potential risk.[20] These clear-cut deficiencies in VasoKINOX remain "uncured".

Under the heading "Finding of prima facie obviousness" on pages 12-14, the Final Office Action addresses the motivation prong of *prima facie* obviousness in three sections, numbered 1-

[20] Leo teaches how to determine when a *patient* should be allowed to decide for him/herself whether to undergo a treatment, so is irrelevant to the issue of a medical provider's evaluating potential benefit vs. potential risk.

3. These are discussed in turn below. The Final Office Action does not explain in these sections how each limitation of any particular claim is either met by, or obvious in view of, the cited art, apparently assuming it is sufficient to rely on the generic discussion of various limitations in the foregoing pages of the Final Office Action (none of which is tied by the Final Office Action to any particular claim), rather than point to specific limitations in specific claims. Applicant will attempt to map the Final Office Action's generic discussions to particular limitations in particular claims in order to demonstrate why the obviousness rejections are unwarranted.

The first numbered section on page 12 addressing "motivation" reads:

> 1. It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to perform the method of VasoKINOX and teach that inhaled NO may/could increase PCWP leading to a potential risk of pulmonary edema, as suggested by Kazerooni et al. and Loh et al. and produce the instant invention.
>
> One of ordinary skill would have been motivated to do this because it is very well known in the art that a PCWP of greater than 20 mm Hg results in edema regardless of how the PCWP is increases and it is also very well known in the art that inhaled NO increases PCWP as taught by Loh et al. Therefore is obvious to teach/warn/instruct the artisan administering iNO therapy that inhaled NO may/could increase PCWP leading to a potential risk of pulmonary edema.

Applicant guesses that this section of the Final Office Acton is meant to apply to claim 1. (If this is not correct, clarification is respectfully requested.) Claim 1 includes many limitations that are not addressed in the quoted section, perhaps because the Office is assuming that the missing limitations are somehow all found in the primary reference, VasoKINOX. Such an assumption would not reflect the facts, as applicant explained in detail above.

Claim 1 as presently amended reads as follows:

> **1. A method of providing a pharmaceutical product, the method comprising:**
>
> **generating a cylinder containing compressed nitric oxide gas by a process comprising compressing nitric oxide and nitrogen gases under high pressure;**
>
> **supplying the cylinder containing compressed nitric oxide gas to a medical provider responsible for treating a plurality of neonates with hypoxic respiratory failure, including some who do not have left ventricular dysfunction and who are not dependent on right-to-left shunting of blood;**
>
> **informing the medical provider that a recommended dose of inhaled nitric oxide gas for treatment of neonates with hypoxic respiratory failure is 20 ppm nitric oxide;**
>
> **providing a first warning to the medical provider that inhaled nitric oxide is contraindicated in the treatment of neonates dependent on right-to-left shunting of blood; and**

providing a second warning to the medical provider, distinct from the first warning, that in patients with pre-existing left ventricular dysfunction, inhaled nitric oxide may increase pulmonary capillary wedge pressure (PCWP), leading to pulmonary edema, the second warning being sufficient to cause a medical provider considering inhaled nitric oxide treatment for a plurality of neonatal patients who (a) are suffering from a condition for which inhaled nitric oxide is indicated, and (b) have pre-existing left ventricular dysfunction, to elect to avoid treating one or more of the plurality of patients with inhaled nitric oxide in order to avoid putting the one or more patients at risk of pulmonary edema.

Each of several deficiencies in the *prima facie* case against claim 1 is described below. *Any one of these deficiencies is sufficient to require withdrawal of the rejection of this claim.*

As previously established by applicant, the Final Office Action has incorrectly concluded that VasoKINOX teaches treating "a form of" hypoxic respiratory failure. It teaches no such thing, instead focusing on a very different condition: pulmonary hypertension in the context of cardiac surgery. One therefore cannot conclude, as the Office has apparently done, that VasoKINOX teaches supplying a cylinder containing compressed nitric oxide gas to a medical provider responsible for treating a plurality of neonates with hypoxic respiratory failure, as required by claim 1. None of the cited references make up for this deficiency, so the rejection fails on that fundamental ground alone. Furthermore, neither VasoKINOX nor the other cited references teaches that 20 ppm is a recommended dose of inhaled nitric oxide for treatment of neonates with hypoxic respiratory failure, so the rejection fails on that ground, as well.

The last paragraph of the claim requires providing a warning (the "second warning") that in patients with pre-existing left ventricular dysfunction, inhaled nitric oxide may increase PCWP, leading to pulmonary edema. Furthermore, the claim requires that this warning be sufficient to cause a medical provider considering inhaled nitric oxide treatment for a plurality of neonatal patients who (a) are suffering from a condition for which inhaled nitric oxide is indicated, and (b) have pre-existing left ventricular dysfunction, to elect to avoid treating one or more of the plurality of patients with inhaled nitric oxide in order to avoid putting the one or more patients at risk of pulmonary edema. The Office apparently believes that these limitations are met by the LVD contraindication in VasoKINOX, combined with the disclosure in Loh et al. about increased PCWP in adult LVD patients who are treated with inhaled nitric oxide, and the disclosure in Kazeroonie et al. that PCWP of 18 to 25 mm Hg is correlated with pulmonary

edema. Such a belief is not warranted. As described in detail above, there was no basis in the art to conclude that the increase in PCWP observed by Loh et al. in *adult* LVD patients, who have stiff, noncompliant left ventricles, would also be seen in *neonatal* LVD patients, who typically have essentially the opposite problem: soft, overly-compliant left ventricles. Even if one can assume that the reason for the LVD contraindication in VasoKINOX was related Loh et al.'s disclosures regarding *adult* LVD patients (an assumption that applicant does not accept, given that there are other reasonable explanations), that certainly does not mean the contraindication was also related to a concern about increasing PCWP in *neonatal* LVD patients. The evidence of record indicates that those of skill in the art did *not* believe that neonatal LVD patients would experience the same sort of increase in PCWP as adult LVD patients, so would *not* have believed that neonatal LVD patients would be at particular risk of pulmonary edema. The presently claimed methods are, of course, concerned solely with neonatal patients.

Furthermore, there is no reason to assume that the LVD contraindication in VasoKINOX had anything to do with a concern about increased PCWP and resulting pulmonary edema in *any* age patient with pre-existing LVD, even in adults. The contraindication could reasonably be interpreted a number of other ways by one of ordinary skill in the art--*not one of which suggests the second warning required by claim 1*. For example, one of ordinary skill in the art, starting with the recognition that VasoKINOX is about use of inhaled nitric oxide in the context of cardiac surgery, could very reasonably interpret the contraindication as limited to that context: e.g., reading it as saying that if a patient emerges from cardiac surgery with a stiff, noncompliant left ventricle, inhaled nitric oxide should not be administered. This is not pre-existing LVD and is not in the context of hypoxic respiratory failure, so is not the situation described in claim 1. Or the contraindication could reasonably be interpreted to mean that patients whose pulmonary hypertension is *caused by* their LVD should not be given inhaled nitric oxide at all, as it will not be effective in relieving the pulmonary hypertension. Again, this is not the situation described in claim 1. It appears that the Office has relied upon hindsight derived from applicant's own disclosure to concoct an interpretation of the LVD contraindication that ignores several alternate interpretations, each of which fits the facts better and so is more likely to be how one of ordinary skill in the art would have interpreted the contraindication.

As indicated in the above-quoted language from the Final Office Action, the Office alleges that all the motivation one of skill in the art would need in order to combine VasoKINOX's teachings with those of Kazerooni et al. and Loh et al. derives from what is essentially the teachings of Kazerooni et al. about PCWP and pulmonary edema and the teachings of Loh et al. that inhaled nitric oxide can increase PCWP in adult LVD patients. Applicant disagrees. Nothing in Kazerooni et al. and Loh et al. provides a motivation to do any of the following, much less all of it: (1) to take a treatment disclosed in VasoKINOX as being solely for pulmonary hypertension *resulting from cardiac surgery*, and employ the treatment instead to treat neonates who have hypoxic respiratory failure; and *also* (2) to take a contraindication that says only "left ventricular dysfunction" without explanation, and alter it to say that, in patients with pre-existing LVD, inhaled nitric oxide may increase PCWP, leading to pulmonary edema; and *also* (3) to do that in a way that is sufficient to cause a medical provider considering inhaled nitric oxide treatment for neonatal patients who have pre-existing LVD to elect to avoid treating one or more of the neonatal patients with inhaled nitric oxide in order to avoid putting them at risk of pulmonary edema---all the while ignoring several crucial facts, including at least: (a) the entirety of VasoKINOX is directed to medical providers who are focused on the cardiac surgery indication, and no other; (b) the "LVD" of VasoKINOX cannot reasonably be read to apply to all LVD patients, since that would exclude many cardiac surgery patients who are routinely successfully treated with inhaled nitric oxide; and (c) none of the most reasonable interpretations of the LVD contraindication in VasoKINOX applies to the patient population recited in the present claims, i.e., neonates with hypoxic respiratory failure and pre-existing LVD. Since the requisite motivation to carry out the claimed method is missing from the cited art, the *prima facie* obviousness rejection of claim 1 fails.

The Final Office Action's second numbered section addressing "motivation" reads:

> 2. It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to perform the method of VasoKINOX and teach determining if the potential benefit of the treatment outweighs the potential risk described in the second warning and treating the patient with LVD with 20 ppm iNO or discontinuing treatment with iNO if pulmonary edema occurs, as suggested by Kazerooni et al., Loh et al., McLaughlin et al. and Leo, and produce the instant invention.

> One of ordinary skill in the art would have been motivated to do this because it is common in the medical arts for the artisan administering the therapy to make benefit/risk assessments on a case by case basis. Patients where the therapy is contraindicated by the distributer of the pharmaceutical product but left with no further options except death may have benefit from administration of iNO. This is a choice by the artisan and perfectly within the realm of an obvious decision by the artisan including the decision to terminate treatment at any time for any reason including if pulmonary edema occurs especially when the art warns of pulmonary edema as a potential adverse event. In the event that Applicant should take the position that the artisan would not administer the iNO to neonatal patients that meet the exclusion criteria of VasoKINOX, have left ventricular [dysfunction] consistent with a PCWP of greater than or equal to 20 mm Hg, because VasoKINOX teaches not to use the product under those conditions (left ventricular [dysfunction]/all forms of pulmonary arterial hypertension), it is the Examiner's position that the artisan in this art is not an automaton (See MPEP 2141.03) and in terms of the patients welfare administration of a therapy is a decision for the medical artisan and the family of the patient to determine and not the distributer of the pharmaceutical product. The distributer may make warnings but the medical artisan and the family of the patient may or may not abide by them depending on the risks and benefits and outcomes for the patient. Consequently, the medical practitioner may make the choice to disregard such warnings when the situation presents itself for the sake of the patient and not the distributer of the pharmaceutical product. (pages 12-13)

The above-quoted section 2 from the Final Office Action alludes in a general manner to concepts that are probably meant to mirror various limitations found in claim 7 (evaluating potential benefit vs. potential risk), claim 8 (evaluating potential benefit vs. potential risk on a case-by-case basis), claim 21 (recommending that, if pulmonary edema occurs, the treatment be discontinued), and claim 26 (discontinuing the treatment due to the patient's pulmonary edema), though none of this is explicitly stated in the Final Office Action. Those claims either depend from claim 1 or include most of the same limitations as claim 1, so applicant's arguments provided above regarding the limitations of claim 1 that are missing from the cited art and the lack of motivation to alter VasoKINOX to arrive at the method of claim 1 apply here, as well. McLaughlin et al. and Leo do nothing to supplement VasoKINOX, Kazerooni et al., and Loh et al. regarding those glaringly missing limitations and motivations discussed above. Indeed, as was detailed above, if McLaughlin et al. has any relevance at all to pulmonary edema (which it does not appear to have), it would be as a *teaching-away* from the presently claimed methods.

The above-quoted text from section 2 includes a statement that reflects a crucial misunderstanding on the part of the Office: "VasoKINOX teaches not to use the product under

those conditions (left ventricular [dysfunction]/all forms of pulmonary arterial hypertension)." As has been explained above, those of skill in the art know that there are many forms of pulmonary arterial hypertension, including some that are not attributable to pulmonary vasoconstriction, and so in which inhaled nitric oxide would be entirely ineffective. (One example discussed previously is particularly relevant: pulmonary arterial hypertension that is *caused by* a patient's LVD.) VasoKINOX teaches treatment of just one very narrowly drawn category of pulmonary arterial hypertension: that which can occur in the context of cardiac surgery. This is not the same as, nor a "form of," hypoxic respiratory failure, the indication recited in the present claims. Accordingly, those of skill in the art would plainly *not* read VasoKINOX as teaching use of inhaled nitric oxide to treat "all forms of pulmonary arterial hypertension." It follows that those of skill in the art would not read the reference as teaching that the LVD contraindication in VasoKINOX applies to "all forms of pulmonary arterial hypertension." Thus, the contraindication may be meant to apply solely to LVD that occurs as a result of cardiac surgery (i.e., *not* hypoxic respiratory failure), or solely to pulmonary arterial hypertension that is caused by a patient's LVD (again, *not* hypoxic respiratory failure), but clearly does *not* apply to "all forms of pulmonary arterial hypertension." The Office has cited no evidence that the contraindication would be read by those of skill in the art as applying broadly to all forms of pulmonary arterial hypertension, an assumption applicant has refuted above. Further, the Office has cited no evidence that the contraindication would be read by those of skill in the art as applying specifically to hypoxic respiratory failure in neonates with pre-existing LVD, as required by the claims.

The Final Office Action's third numbered section addressing motivation reads:

> 3. It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to perform the method of VasoKINOX and teach performing echocardiography to identify a neonate who is a candidate for iNO treatment and discontinuing treatment due to hypotension or monitoring for evidence of an increase in PCWP or pulmonary edema during treatment, as suggested by Kazerooni et al. and Loh et al., Leo, McLaughlin et al. and Himashree et al., and produce the instant invention.
>
> One of ordinary skill in the art would have been motivated to do this because as taught by Loh et al. and McLaughlin et al., echocardiography is an essential screening tool to assess the patient for left ventricular function, an exclusion criteria in the method

> of VasoKINOX, and Himashree et al. direct the artisan to monitor the patient for adverse events such as systemic hypotension and, as taught by Kazerooni et al. and Loh et al. and increase in PCWP over 20 mm Hg which would be indicative of edema which is a symptom of PAH as taught by Mclaughlin et al.[21] and thus the ordinary artisan would be cognizant of this adverse event and monitor for it in at least one patient. Thus, it is obvious for the artisan to monitor for edema, hypotension and any other possible adverse event due to the administration of iNO for the patient's benefit and discontinue treatment due to the patient's hypotension or any other adverse event that places the patient's safety at risk. This is just common sense. (pages 13-14)

The above-quoted section 3 from the Final Office Action alludes in a general manner to concepts that are probably meant to mirror various limitations found in claim 21 (recommending that, if pulmonary edema occurs, the treatment be discontinued), claim 26 (discontinuing the treatment), and claims 31 and 32 (monitoring for evidence of increased PCWP and/or pulmonary edema during treatment). (The claims reciting hypotension have been canceled, so that aspect of the rejection is moot.) It is not clear why the Office mentions "performing echocardiography," as this is not an element of any of the claims of this application, either as originally presented or as presently amended. If this is meant to correspond to the claim term "performing at least one diagnostic process to identify a first neonate patient who has hypoxic respiratory failure and is a candidate for 20 ppm inhaled nitric oxide treatment" that appears in claim 7 and in slightly altered form in claims 8 and 26, applicant disagrees that this limitation of claims 7, 8 and 26 is taught by any of the art, since none of the cited art teaches anything about hypoxic respiratory failure, much less performing a diagnostic process to identify a neonate who has this condition and so is a candidate for treatment with 20 ppm inhaled nitric oxide. As has been discussed at length above, VasoKINOX is about pulmonary hypertension *in the context of cardiac surgery--**and solely in that context***. Hypoxic respiratory failure is a distinctly different condition. The Office goes on to assert that the art discloses echocardiography as a screening tool for assessing LVD, implying that this use, and not identifying a patient who has hypoxic respiratory failure, is why the Office views the echocardiography disclosure as pertinent to the claims. The claims

[21] Applicant points out for the record that this misinterprets McLaughlin et al.'s use of the term "edema". As established above, McLaughlin was talking about *peripheral* edema (e.g., of the lower extremities), and not *pulmonary* edema. Pulmonary edema is not a "symptom" of pulmonary arterial hypertension—and if it were, then one would expect it to be *alleviated*, not worsened, when inhaled nitric oxide alleviates the patient's pulmonary arterial hypertension. The Office's reliance on McLaughlin is therefore misplaced. None of the cited art suggests an expectation in the art that neonates with LVD might be susceptible to pulmonary edema, such that one would need to "monitor" for this condition.

don't specify any step of assessing LVD, whether by echocardiography or otherwise. Thus, there would seem to be no reason to even bring up the subject of echocardiography. Clarification is respectfully requested.

All of the claims that appear to be implicated by the above-quoted section 3 either depend from claim 1 or include most of the same limitations as claim 1, so applicant's arguments provided above regarding (a) the limitations of claim 1 that are missing from the cited art, and (b) the lack of motivation in the art to alter VasoKINOX to arrive at the method of claim 1, apply here as well. McLaughlin et al., Leo, and Himashree et al. do nothing to supplement VasoKINOX, Kazerooni et al., and Loh et al. regarding those glaringly missing limitations and motivations discussed above in the context of claim 1.

The Final Office Action at page 14 provides a single sentence addressing the second prong of prima facie obviousness, i.e., the requirement that a reasonable expectation of success be found in the art:

> From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

Applicant strongly disagrees with this sweeping conclusion, and notes that the Office does not attempt to explain how it is "apparent" from the teachings of the references. Certainly the references themselves do not support the Office's conclusion. Applicant has explained how the references do not address hypoxic respiratory failure at all. Nor do the references suggest there is any link between pre-existing LVD in a neonate and a risk of pulmonary edema upon treatment with inhaled nitric oxide. Without such a link, there is no reason to expect that the second warning specified in the claims would be successful in reducing the risk of pulmonary edema in neonates with hypoxic respiratory failure and LVD.

Highly relevant to any obviousness inquiry is evidence of objective considerations pertaining to the question of what would have been obvious to one of ordinary skill in the art. See, for example, pages 15-16 of the recent Federal Circuit case *Plantronics, Inc. v. Aliph, Inc.*, slip op. 2012-1355 (decided July 31, 2013), where the court noted that "relevant objective considerations" constitute one of the four underlying factual inquiries (i.e., "Graham factors")

that *must* be considered by a fact finder prior to determining obviousness. In the present case, there are a number of lines of objective evidence illustrating that, until the present inventors made their discovery, those of ordinary skill in the art (indeed, even those of extraordinarily high skill in the art) did not know that neonates with LVD might be at any risk of pulmonary edema when treated with inhaled nitric oxide, and would not have read VasoKINOX as stating that there was such a risk. That evidence is summarized below.

VasoKINOX's disclosure is based entirely on information known in the art as of April 5, 2007

VasoKINOX appears to have been published on or after July 14, 2008, the date on the first page of the cover letter from the Belgian authorities issuing a marketing authorization to Air Liquide Sante International for the VasoKINOX product. The marketing authorization stemmed from an approval of the product by the European Union's Federal Agency for Drug and Medical Products (the "Agency") dated the same date. See the Public Assessment Report ("Report") published in connection with the marketing approval of VasoKINOX by the Agency, a copy of which is included in the Information Disclosure Statement filed with this Reply.) The Report comments on the registration dossier that was submitted to the Agency in connection with Air Liquide's application for marketing approval of VasoKINOX nitric oxide gas.

As can be gleaned from the Report, the VasoKINOX application for marketing approval relied on safety and efficacy data that had been published prior to the time the VasoKINOX application was filed with the Agency (which, according to the "Timetable" on pages 5-6 of the Report, was April 5, 2007), and not on any new clinical trial that uncovered some hitherto unknown effect. For example, page 5 of the Report under "Type of application" says that the VasoKINOX application concerns "a stand-alone application […] related to medicinal products containing constituent(s) with a well established medicinal use, with recognized efficacy and an acceptable level of safety, **by means of a detailed scientific bibliography**" [emphasis added]. Section I.9 on page 30 of the Report confirms that "no specific clinical studies have been conducted with nitric oxide." Section I.10 on page 30 notes that Air Liquide "has not performed any new pharmacokinetic (pK) or pharmacology (pD) studies on inhaled nitric oxide (iNO)," instead relying on the "available literature." Section I.11 on pages 30-31 likewise refers to previously reported results regarding pharmacodynamics of inhaled nitric oxide. Section I.12 on

page 31 summarizes results of 17 published studies in support of the clinical efficacy of inhaled nitric oxide. Section I.13 on page 32 refers to "the studies"—an apparent reference to the previously published studies summarized in Section I.12—in describing the clinical safety of the product. Thus, it is clear that all of the clinical and safety information contained in the VasoKINOX "disclosure" is based on information that had been published by various entities prior to April 5, 2007. As will be discussed below, those of ordinary skill in the art in 2007 were unaware that neonates with LVD should be excluded from treatment with inhaled nitric oxide, and did not learn this fact until the results of applicant's INOT22 study were published. Thus, at the present application's June 30, 2009 priority date, the listing of "left ventricular dysfunction" as a contraindication in VasoKINOX would not have been read as a general warning that neonates with pre-existing LVD are at risk of pulmonary edema (or anything else) upon treatment with inhaled nitric oxide.

The risk of pulmonary edema in neonates was unexpected prior to the INOT22 study

Beginning in 2004, INO Therapeutics LLC ("INOT") sponsored a clinical trial formally 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" and known as the INOT22 study. The purpose of the study was to assess the safety and effectiveness of inhaled nitric oxide as a diagnostic agent in pediatric patients undergoing assessment of pulmonary hypertension (primary objective), and to confirm the hypothesis that inhaled NO is selective for the pulmonary vasculature (secondary objective).[22]

The INOT22 study was a randomized, multi-center study having an expected total enrollment of 150 patients in approximately 18 study sites over approximately 2 years.[23] According to Dr. Baldassarre, the expected patient population for enrollment into the study was subjects between the ages of 4 weeks and 18 years with idiopathic pulmonary arterial hypertension, congenital heart disease with pulmonary hypertension, or a cardiomyopathy, and

[22] Baldassarre 132 Declaration, ¶ 6, 7.
[23] *Id.* ¶ 7.

who were undergoing diagnostic right heart catheterization scheduled to include acute pulmonary vasodilation testing to assess pulmonary vasoreactivity."[24]

The INOT22 study was designed by INOT and a Steering Committee made up of internationally recognized experts in the field of pediatric heart and lung disease.[25] The Steering Committee consisted of:

a. **David L. Wessel, MD**, presently Senior Vice President, The Center for Hospital Based Specialties at Children's National Medical Center, Washington, DC;

b. **Robyn J. Barst, MD**, most recently Professor Emeritus of Pediatrics and Medicine, Columbia University College of Physicians and Surgeons, New York (now deceased); and

c. **Duncan J. Macrae, MD**, presently Director, Pediatric Intensive Care, Royal Brompton Hospital, London, U.K.[26]

The original exclusion criteria for the INOT22 study did **not** exclude patients with pre-existing left ventricular dysfunction who are not dependent on right-to-left shunting of blood.[27] In particular, the original INOT22 study protocol contained the following inclusion and exclusion criteria:

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 [Congenital Heart Disease] 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

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[24] *Id.*
[25] *Id.* ¶ 8.
[26] *Id.* ¶ 9.
[27] *Id.* ¶ 10.

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).

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 +).[28]

The original INOT22 study investigational plan and study protocol were reviewed and approved by the Institutional Review Board (IRB) and/or Independent Ethics Committee (IEC) at each of the 18 participating study institutions, including review by the principal investigator within each study institution.[29] The original study protocol was also reviewed by experts at FDA and each National Health Authority (European equivalent to FDA) within the four European countries participating in the INOT22 study: United Kingdom, France, Netherlands, and Spain.[30] In addition, INOT regularly requested input and scientific guidance on clinical trials, such as the INOT22 study, from its own Scientific Advisory Board (SAB).[31]

At no time did the study sponsor, any of the experts on the Steering Committee, any of the principal investigators, any of the IRBs, any of the IECs, any of the SAB members, any of the FDA experts, or any of the European Health Authority experts (altogether estimated to total at least 115 medical professionals) suggest that the exclusion criteria for the INOT22 study protocol be amended to exclude patients who have LVD but were not dependent on a right-to-left shunt.[32] **In other words, of the estimated 115+ medical professionals tasked with the**

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[28] *Id.*
[29] *Id.* ¶ 11.
[30] *Id.*
[31] *Id.*
[32] *Id.*

duty to consider potential safety issues for INOT22 study patients, none—*not a single one*--suggested there was a chance that inhaled nitric oxide might increase the likelihood of pulmonary edema in neonates who have LVD.[33]

Upon administration of inhaled nitric oxide to the first 24 subjects enrolled in the INOT22 study, five serious adverse events (SAEs) were recorded – a rate much higher than expected based on prior clinical experience with inhaled nitric oxide. Each of these five SAEs was a cardiovascular event, such as pulmonary edema, cardiac arrest or hypotension (low blood pressure).[34]

In February 2005, INOT and the Steering Committee convened to review the unexpected SAEs described above, and upon review and discussion, amended the exclusion criteria of the INOT22 study protocol to thereafter exclude subjects from enrollment if they demonstrated an elevated pulmonary capillary wedge pressure (PCWP), defined within the study as subjects having a PCWP greater than 20 mmHg, a symptom of LVD. All study sites were notified immediately.[35]

After conclusion of the study, analysis of the data revealed that modification of the exclusion criteria significantly reduced the rate of serious adverse events (including serious adverse events associated with heart failure). This analysis demonstrated that there were 5 SAEs among the first 24 subjects (i.e., those enrolled prior to amendment of the exclusion criteria), but only 2 SAEs among the next 80 subjects in the study (i.e., enrolled after amendment of the exclusion criteria). Further analysis of the data showed that a total of four subjects had pre-existing LVD, and of these four, two (i.e., 50%) experienced SAEs. Of the 120 subjects *not* found to have evidence of LVD, only 4% experienced SAEs. This result was unexpected and came as a great surprise to those working on the study.[36]

<u>Over 100 medical professionals did not find the claimed methods to be obvious</u>

More than one hundred other medical professionals belonging to the IRBs and IECs at each of the 18 medical institutions in the United States and Europe that participated in the study

[33] *Id.* ¶¶ 11, 14.
[34] *Id.* ¶ 15.
[35] *Id.* ¶ 16.
[36] *Id.* ¶ 17.

did not find the claimed methods to be obvious. Each of these IRBs and IECs, as well as the principal investigator within each study institution, reviewed the original INOT22 study protocol design prior to study initiation and enrollment.[37]

FDA regulations require an IRB to comprise a group of professionals appropriately constituted and formally designated to review and monitor biomedical research involving human subjects. In accordance with FDA regulations, an IRB has the authority to approve, require modifications in (to secure approval), or disapprove research. This group review serves an important role and responsibility in the protection of the rights and welfare of human research subjects and in ensuring that appropriate steps are taken to protect human subjects participating in clinical research. An IRB must have at least five members, and each member must have enough expertise to make an informed decision on whether the research is ethical, the informed consent is sufficient, and the appropriate safeguards to protect patient safety have been put in place prior to starting a clinical trial.[38]

In Europe, the analog of an IRB is an IEC, an independent body consisting of healthcare professionals and non-medical members whose responsibility is to protect the rights, safety, and wellbeing of human subjects involved in a clinical trial and to provide public assurance of that protection by expressing an opinion on a proposed clinical trial protocol, the suitability of the investigators, and the adequacy of facilities involved in a trial. Like an IRB, an IEC will review a clinical trial protocol with the intent of protecting patient safety prior to clinical enrollment.[39]

In sum, IRBs and IECs are composed of qualified medical professionals tasked with reviewing all clinical trial protocols proposed at their respective institutions and empowered to make or suggest changes to a given protocol that are deemed necessary to best ensure patient safety during the clinical trial. *Naturally, any obvious safety concerns arising from a proposed clinical trial protocol will be identified by an IRB/IEC and the protocol will be amended to avoid obvious and unnecessary clinical risks.*[40] *If a given safety issue is not flagged by the reviewing IRB/IEC, it by definition is not obvious to the members of the IRB/IEC.*

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[37] *Id.* ¶ 11.
[38] *Id.* ¶ 12.
[39] *Id.* ¶ 13.
[40] *Id.* ¶¶ 11-14.

Officials of FDA and four European Health Authorities did not find the claimed methods to be obvious

As further evidence that those of skill in the art did not consider the claimed methods to be obvious, applicant notes that FDA did not require the INOmax drug label to include a warning or exclusion for patients with LVD until after applicant discovered the risk to this population. Furthermore, FDA and four European Health Authorities who reviewed the original INO22 Study protocol did not flag any risk to such patients.

Inhaled NO was approved as a drug by FDA in December 1999, after extensive clinical study and FDA review.[41] Upon approval, and up to the time the present invention was made, the INOmax® label[42] contained language communicating, in pertinent part, the following general warnings and contraindication:

> *INOmax® 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....*
>
> *Methemoglobinemia increases with the dose of nitric oxide. ... Following discontinuation or reduction of nitric oxide the methemoglobin levels returned to baseline over a period of hours....*
>
> *INOmax should be administered with monitoring for PaO_2, methemoglobin and NO_2....*
>
> *INOmax® should not be used in the treatment of neonates known to be dependent on right-to-left shunting of blood.*

Thus, the original INOmax® label did not include any warning or precaution with respect to a risk of pulmonary edema in patients with pre-existing LVD, and in fact was entirely silent about the latter.[43]

Moreover, neither FDA nor other National Health authorities reviewing the original protocol for the INOT22 study suggested that patients with LVD should be excluded from this

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[41] *Id.* ¶ 4.
[42] *Id.* ¶ 5.
[43] *Id.* After approval by FDA, INOmax® was also approved for use in Europe, Canada, Australia, Mexico and Japan by the National Health Authorities of those countries. Like the U.S. label, the original INOmax® drug labels in those countries did not contain any warning or precaution regarding patients with LVD.

study.[44] Not a single individual in any of these regulatory organizations suggested that administering inhaled nitric oxide to children with LVD might lead to an increased risk of adverse events such as pulmonary edema.[45]

The evidence shows, however, that FDA did require a label change upon being notified by the INOT22 study sponsor of the newly discovered risk to children with LVD.[46] Upon conclusion of the INOT22 study and completion of the final study report, applicant discovered that children with LVD are at increased risk for adverse events, including pulmonary edema. Because this was an important and unexpected finding, INOT submitted a label supplement to FDA on February 25, 2009, seeking to amend the prescribing information for INOmax® to include a warning statement for physicians.[47] On August 28, 2009, FDA approved the INOmax® label supplement that included the following new information:

> *WARNINGS AND PRECAUTIONS*
>
> *Heart Failure: In patients with pre-existing left ventricular dysfunction, inhaled nitric oxide may increase pulmonary capillary wedge pressure leading to pulmonary edema (5.4).*
>
> *5 WARNINGS AND PRECAUTIONS*
>
> *5.4 Heart Failure: Patients who had pre-existing left ventricular dysfunction treated with inhaled nitric oxide, even for short durations, experienced serious adverse events (e.g., pulmonary edema).*[48]

Thereafter, similar warnings were added to the INOmax® label in Japan, Europe, Canada and Australia.[49]

The above facts establish that, prior to applicant's 2009 priority date, medical professionals working in the real world did not exclude neonates with LVD from inhaled nitric oxide therapy. Over 100 experts worldwide and the regulatory authorities of five countries considered what patient populations to exclude from the INOT22 study when it was originally

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[44] Baldassarre 132 Declaration, ¶ 11.
[45] *Id.*
[46] *Id.* ¶ 18.
[47] *Id.*
[48] *Id.*
[49] *Id.*

designed, and did not suggest excluding children with LVD from that study. Their actions definitively demonstrate an assumption in the art that children with LVD can safely inhale nitric oxide. Given that, as established above, the substance of the VasoKINOX application was based on information published prior to April 5, 2007, Applicant submits that a person of ordinary skill in the art before the present application's priority date would have interpreted all aspects of VasoKINOX, including the LVD contraindication, in a way that is consistent with what was known in the art prior to April 5, 2007—i.e., consistent with an understanding that children with LVD can safely inhale nitric oxide without an increased risk of pulmonary edema. That person of ordinary skill would not have interpreted VasoKINOX as announcing a startling new finding, inconsistent with generally accepted assumptions in the art, that neonates with hypoxic respiratory failure and LVD are at risk of pulmonary edema when treated with inhaled nitric oxide. Any of the alternate readings of the VasoKINOX contraindication supplied by applicant above would be more reasonable and consistent with the evidence than is the one promoted by the Final Office Action, suggesting that the views expressed in the Final Office Action about what is "obvious" are based on the teachings of the present application, rather than the art.

CONCLUSION

In sum, applicant has provided myriad reasons the obviousness rejection should be withdrawn, any one of which is sufficient to require withdrawal of the rejection. For example, the primary reference cited in the rejection (VasoKINOX) does not qualify as prior art, so is not properly citable as part of an obviousness rejection made against the present claims. In addition, the Office has not established a *prima facie* case of obviousness against the presently claimed methods in view of VasoKINOX, Kazerooni et al., Loh et al., Leo, Himashree et al., and McLaughlin et al. To wit: the Office has misconstrued many of the teachings of the cited art in significant ways, has failed to take into account how a person of ordinary skill in the art at the filing date would have interpreted the teachings, and has established neither a motivation to carry out the claimed methods nor a reasonable expectation of success upon doing so. Accordingly, for multiple reasons—any one of which is sufficient—the rejection should be withdrawn.

Applicant asks that all rejections be withdrawn and the claims as presently amended be allowed. If any issues remain, the Examiner is invited to telephone the undersigned at 617-521-7037 to discuss.

Apply any necessary charges, or any credits, to deposit account 06-1050, referencing attorney docket number 26047-0003006.

Respectfully submitted,

Date: December 23, 2013

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

Customer Number 94169
Fish & Richardson P.C.
Telephone: (617) 521-7054
Facsimile: (877) 769-7945

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EXHIBIT A

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	: James S. Baldassarre	Art Unit	: 1613
Serial No.	: 13/683,236	Examiner	: Ernst V. Arnold
Filed	: November 21, 2012	Conf. No.	: 5655
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. 13/683,236 (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 divisional 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 divisional 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"[1], which was cited in a rejection by the U.S. Patent and Trademark Office in an Office action dated April 24, 2013 in the present application. The VasoKINOX document bears the date of July 14, 2008.

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

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

6. As evidence of my date of invention, I have attached photocopies of an early INOT22 study protocol "Amendment I" (Appendix 1); an electronic exchange between me and members of the INOT22 study steering committee (Appendix 2); a further amended "Amendment II" INOT22 study protocol (Appendix 3); a letter from INOT to the U.S. Food and Drug Administration ("FDA") (Appendix 4); an electronic exchange between me and Debra A. Rimar

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

with a draft Clinical Study Report[2] attached (Appendix 5); and the prescribing information for INOmax® (nitric oxide) for inhalation published in 2007 (Appendix 6). Certain material irrelevant to the question of date of invention has been redacted from Appendices 2, 4, and 5. In the remaining material of Appendices 2, 4, and 5, and in Appendices 1 and 3, all dates have been redacted; all of these redacted dates are prior to July 14, 2008.

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

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

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

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: 12/11/2013

James S. Baldassarre, M.D.

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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 ≥ 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%)

5. ETHICS

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

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

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

5.2 Ethical Conduct of the Study

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

5.3 Patient Information and Informed Consent

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

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

5.4 Financial Interest Statement

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

6. INVESTIGATORS AND STUDY ADMINISTRATION STRUCTURE

6.1 Investigators

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

6.2 Administrative Structure

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

6.3 Steering Committee Members

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

6.4 Data Safety and Monitoring Board Members

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

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

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

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

7. INTRODUCTION

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

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

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

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

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

8. STUDY OBJECTIVES

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

Patients with Idiopathic Pulmonary Arterial Hypertension or patients with CHD who do not have an unrestricted shunt at the level of the ventricle or ductus arteriosus, response will be defined as:

1) a decrease in PAPm $\geq$ 20% and no decrease in cardiac index (within 5%)

Patients with cardiomyopathy or patients with CHD who have an unrestricted shunt at the level of the ventricle or ductus arteriosus, response will be defined as:

1) a decrease in PAPm $\geq$ 20% and no decrease in cardiac index (within 5%)

or

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

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

9. INVESTIGATIONAL PLAN

9.1 Overall Study Plan and Design

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

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

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

9.2 Discussion of Study Design

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

9.3 Selection of Study Population

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

9.3.1 Inclusion Criteria

The patient must meet the following criteria:

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

c. Cardiomyopathy

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

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

9.3.2 Exclusion Criteria

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

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

9.3.3 Removal of Patients from Therapy or Assessment

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

9.4 Treatments

9.4.1 Treatments Administered

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

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

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

9.4.2 Identity of Investigational Product

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

9.4.3 Method of Assigning Patients to Treatment Groups

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

9.4.4 Selection of Doses in the Study

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

9.4.5 Selection and Timing of Dose for Each Patient

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

9.4.6 Treatment Group Assignment Blinding

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

9.4.7 Prior and Concomitant Therapy

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

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

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

9.4.8 Treatment Compliance

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

9.5 Efficacy and Safety Variables

9.5.1 Efficacy and Safety Schedule of Assessments

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

Table 1. Schedule of Assessments

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

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

Table 2. Schedule of Treatments

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

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

9.5.2 Data Collection

Baseline Measurements

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

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

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

Measurements Following First Treatment Administration

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

Measurements Following Second Treatment Administration

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

Measurements Following Third Treatment Administration

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

Measurements 1 year after the diagnostic procedure

- Therapies received since the diagnostic procedure

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

Procedures for Maintenance of Baseline Oxygen Saturation Levels

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

Awake Sedation Patients

Patients Not on Supplemental O_2

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

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

Patients on Supplemental O_2

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

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

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

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

Patients Intubated and Under General Anesthesia

Patients Not on Supplemental O_2

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

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

Patients on Supplemental O_2

1. Before intubation and initiation of general anesthesia, obtain patients baseline oxygen saturation levels (pulse oximetry) with patient's supplemental oxygen in place.
2. Patients will be placed under general anesthesia and intubated according to the standard medical care and procedures of the institution.
3. Right heart catheterization
4. Adjust the patient's O_2 to match delivery they were receiving through nasal cannula prior to study enrollment.

2. Re-check patient's O_2 saturation level. It should be the same as initial value, if not, adjust the blender accordingly.
3. Note analyzed O_2 reading from INOvent.
4. Allow for a 10-minute equilibrium period.
7. Take baseline hemodynamic measurements.
8. Start first treatment (80 ppm or 100% O_2 as per randomization table).
9. After 1 minute adjust oxygen blender to maintain baseline SpO_2.
10. Maintain treatment for 10 minutes.
11. Take hemodynamic measurements.
12. Start second treatment by adding either 80 ppm NO or 100% O_2 so that the administered treatment is a combination of 80 ppm NO and 100% O_2.
13. After 1 minute adjust oxygen blender to maintain baseline SpO_2.
14. Maintain treatment for 10 minutes.
15. Take hemodynamic measurements.
16. Stop treatment.
17. Adjust oxygen blender to maintain patient's baseline SpO_2.
18. Ten minute wash out period
19. Take baseline hemodynamic measurements
20. Start third treatment of either 80 ppm NO or 100% O_2. The third treatment will be whichever study gas was not administered during the first treatment period.
21. Adjust oxygen blender to maintain patient's baseline SpO_2.
22. Maintain treatment for 10 minutes.
23. Take hemodynamic measurement.
24. Stop treatment.
25. Adjust oxygen blender to maintain patient's baseline SpO_2.
26. Allow for a ten-minute equilibrium period.
27. Extubation will occur as per each institutions standard of care.

9.5.3 Ventilator Weaning and Extubation Strategy

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

9.5.4 Appropriateness of Measurements

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

9.5.5 Efficacy Variables

Primary endpoint:

Number of patients receiving a combination of NO and O_2 versus the number of patients receiving O_2 alone that meet response criteria. The response criteria are as follows:

Patients with Idiopathic Pulmonary Arterial Hypertension or patients with CHD who do not have an unrestricted shunt at the level of the ventricle or ductus arteriosus, response will be defined as:

1) a decrease in PAPm $\geq$ 20% and no decrease in cardiac index (within 5%)

Patients with cardiomyopathy or patients with CHD who have an unrestricted shunt at the level of the ventricle or ductus arteriosus, response will be defined as:

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

or

2) a decrease in PVRI ≥ 25% and no decrease in cardiac index (within 5%)

Secondary endpoints:

1) Number of patients receiving NO versus the number of patients receiving O_2 that meet response criteria, as defined above.

2) Number of patients receiving a combination of NO and O_2 versus the number of patients receiving NO alone that meet response criteria, as defined above.3) PVRI, PAPm and Cardiac Index readings in Room Air versus NO alone, O_2 alone and the combination of NO and O_2.

4) Change in the ratio of PAPm to SAPm by treatment

5) Survival at 1 year, by response

9.5.6 Safety Variables

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

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

9.5.7 Drug Concentration Measurements

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

9.6 Data Quality Assurance

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

9.7 Statistical Methods Planned and Determination of the Sample Size

See Appendix 2.

9.7.1 Sample Size Determination

The following assumptions are made:

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

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

9.7.2 Interim Analysis

No interim analysis is planned for this trial.

9.8 Changes in Conduct of the Study or Planned Analyses

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

10. ADMINISTRATIVE DETAILS

10.1 Accountability of Study Drug and Equipment

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

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

10.2 Case Report Forms

All case report forms are to be completed within one month after patient completion of the study. A case report form is provided for each patient. All forms are to be filled out in black ink or typed.

Correction(s) of data on the case report form should be made by crossing out the incorrect data (in a manner that leaves the previous entry identifiable) and writing the correct values next to those crossed out. Each correction must be initialed and dated by the individual making the correction.

10.3 Investigator Requirements

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

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

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

10.4 Recording of Adverse Events

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

10.4.1 Study Drug Relationship

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

Not Related

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

Remote

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

Possible

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

Probable

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

Highly Probable

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

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

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

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

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

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

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

10.4.2 Serious Adverse Events

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

Catherine Evans

INO Therapeutics Regualtory Affairs Associate

Phone: +001 908 238-6655

Fax: +001 908 238-6635

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

James S. Baldassarre, MD

INO Therapeutics Senior Director of Research & Development

Phone: +001 908 238-6363

Cell: +001 908 500-8111

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

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

10.4.3 Unexpected Adverse Events

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

10.5 Records Retention

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

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

10.6 Monitoring and Audits

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

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

10.7 Amendments to the Protocol

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

10.8 Termination of Trial

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

11. REFERENCE LIST

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

APPENDIX 1. PROTOCOL VERSIONS

Protocol Versions:

[redacted]

APPENDIX 2. ANALYTIC PLAN

A. Analysis Populations

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

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

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

B. Analyses of Baseline Characteristics

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

C. Primary Efficacy Analysis

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

Patients with Idiopathic Pulmonary Arterial Hypertension or patients with CHD who do not have an unrestricted shunt at the level of the ventricle or ductus arteriosus, response will be defined as:

1) a decrease in PAPm $\geq$ 20% and no decrease in cardiac index (within 5%)

Patients with cardiomyopathy or patients with CHD who have an unrestricted shunt at the level of the ventricle or ductus arteriosus, response will be defined as:

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

or

2) a decrease in PVRI ≥ 25% and no decrease in cardiac index (within 5%)

These variables will be calculated as follows:

% Change in PAPm from Baseline =

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

% Change in PVRI from Baseline =

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

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

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

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

The alternative hypothesis is:

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

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

D. Secondary Efficacy Analysis

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

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

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

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

The alternative hypothesis is:

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

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

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

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

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

The alternative hypothesis is:

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Change in the Ratio of PA Pressure to Systemic Pressure

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

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

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

Survival at 1 Year Following the Diagnostic Procedure

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

H_o: There is no difference in the survival rate of patients with a positive response in PAPm or PVRI between the NO and O_2 group versus the O_2 alone group.
The alternative hypothesis is:
H_a: A difference exists in the survival rate of patients with a positive response in PAPm or PVRI between the NO and O_2 group versus the O_2 alone group.

The difference between the two treatment groups will be tested using the Fisher's Exact Test. This test will be conducted with the type I (α) error of 0.05 for statistical significance (2-tailed). In addition, a Kaplan-Meier plots will be generated for time to death for each treatment group.

E. Safety Analysis

Serious Adverse Events

The analysis will be performed on the number and types of serious adverse events reported in each treatment group. The incidence of all serious adverse events, stratified by MEDRA terms, MEDRA body system, and patients with specific serious adverse events will be tabulated. Additionally, the serious adverse events will be stratified by age, sex and race.

H_o: There is no difference in the number of reported serious adverse events between the NO, NO + O_2 and O_2 alone groups.

H_a: A difference exists in the number of reported serious adverse events between the NO, NO + O_2 and O_2 alone groups.

This comparison will be made using Cochran's Test for Related Observations.

Drug Related Adverse Events

The analysis will be performed on the number and types of drug related adverse events reported in each treatment group. The incidence of all drug related adverse events, stratified by MEDRA terms, MEDRA body system, and patients with specific adverse events will be tabulated. Additionally, the adverse events will be stratified by age, sex and race.

H_o: There is no difference in the number of reported drug related adverse events between the NO, NO + O_2 and O_2 alone groups.

H_a: A difference exists in the number of reported drug related adverse events between the NO, NO + O_2 and O_2 alone groups.

This comparison will be made using Cochran's Test for Related Observations.

F. Additional Analyses

All primary methods of analysis have been previously outlined in this document. However, INO Therapeutics reserves the right to perform any additional analyses deemed necessary according to any of the following reasons:

1. Any steering committee or medical monitor recommendations based on investigator concerns.
2. The presence of maldistributed baseline characteristics.
3. The administration of any medications thought to be affecting the treatment as determined by the steering committee and/or the medical monitor.

Additionally, several exploratory analyses will be conducted to determine the existence of any possible relationships between the response variables and diagnosis, delivery system, demographic criteria, etc. Due to the unknown nature of these analyses, INO Therapeutics, Inc. declines to formalize the testing procedures in this analytic plan.

G. Interim Analyses

No interim analysis for efficacy or safety in this study is planned.

APPENDIX 3. LISTING OF AMENDMENT CHANGES

AMENDMENT 1 CHANGES:

Cover Page, Version

Changed From:

"Original Protocol"

Changed To:

"Amendment 1"

Cover Page, Document Date

Changed From:

[redacted]

Changed To:

[redacted]

Cover Page, Study Contact

Deleted: Paul Bridges, European Regulatory Affairs

Changed From:

"Rebecca Light, Clinical Research Manager"

Changed To:

"Jodee Newman, Project Leader"

Synopsis

Changed From:
"Sponsor-INO Therapeutics, Inc."

Changed To:
"Sponsor-INO Therapeutics, LLC"

Changed From:
"Investigators-TBD"

Changed To:
"Investigators- Pr. Daniel Sidi,, Dr. Alain Fraisse, Dr. Federico Larraya, Dr. Jose Luis Zunzunegui, Dr. Joaquin Jose Bartrons, Prof. Dr. Rolf Berger, Dr. Alan Magee, Dr. Mary Mullen, Dr. Robyn Barst "

Changed From:
"Study Centers-TBD"

Changed To:
Study Centers-Hopital Necker, Paris, France; CHU la Timone-Hopital d'enfants, Marseille, France; Hospital Materno-Infantil XII de Octubre, Madrid, Spain; Hospital Gregorio Maranon, Madrid Spain; Hospital Sant Joan de Deu, Barcelona, Spain; Beatrix Children's Hospital, Univ. Hospital Groningen, Amsterdam, Netherlands; The Royal Brompton Hospital, London, UK; Boston Children's Hospital, Boston, MA, US; Columbia Presbyterian Hosptital, New York, NY, US

Secondary Endpoints-Addition:

4) Change in the ratio of PAPm to SAPm by treatment

6) Survival at 1 year by response

4. List of Abbreviations and Definitions of Terms

Addition:
Mean Systolic Arterial blood pressure

Page 14 Section 9.1

Addition:
"Following the acute diagnostic procedure, a brief follow up contact will be made on each patient to determine the vital status 1 year after the diagnostic procedure."

Section 9.5.1 Table 1 - Footnote

Addition:
Assessment-Baseline :Arterial pH
Follow up assessment at 1 yr. Will consist of telephone call to assess medical therapies or surgical procedures pertaining to pulmonary/cardiac disease, and vital status /date of death if applicable.

9.5.2 Data Collection

Addition:
Of Arterial pH to-

Baseline Measurement and Measurements Following Third Treatment Administration

Measurements 1 year after the diagnostic procedure

- Therapies received since the diagnostic procedure
- Date of surgery (if any)
- Vital status and date of death, if applicable

9.5.5 Efficacy Variables

Secondary Endpoints-Addition:

4) Change in the ratio of PAPm to SAPm by treatment

7) Survival at 1 year by response

10.4.2 Serious Adverse Events

Changed From:
Any serious adverse event must be reported to INO Therapeutics within 24 hours by telephone to:

Catherine Evans, Regulatory Affairs Associate

Phone: (908) 238-6655

Fax: (908) 238-6635

Dr. James S. Baldassarre

Phone: (908) 238-6363 Cell: (908) 500-8111

Changed To:
All serious adverse events occurring during the study, and within 12 hours of the discontinuation of treatment gas, or hospital discharge whichever comes first, must be reported within 24 hours to INO Therapeutics by fax/telephone to:

Catherine Evans

INO Therapeutics Regulatory Affairs Associate

Phone: + 001 908 238-6655

Fax: +001 908 238-6635

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

Dr. James S. Baldassarre

Phone: +001 908 238-6363

Cell: +001 908 500-8111

Added to text: *"within 24 hours by completing an SAE packet with"*

Delete page 40, second to last paragraph:

All patient/subject deaths will be reported independent of the temporal relationship to the patient's/subject's study participation and treatment (i.e. test drug, placebo).

Appendix 2. Analytic Plan

Section D-page 42/43 Addition:

Change in the Ratio of PA Pressure to Systemic Pressure

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

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

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

Survival at 1 Year Following the Diagnostic Procedure

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

H_o: There is no difference in the survival rate of patients with a positive response in PAPm or PVRI between the NO and O_2 group versus the O_2 alone group.
The alternative hypothesis is:
H_a: A difference exists in the survival rate of patients with a positive response in PAPm or PVRI between the NO and O_2 group versus the O_2 alone group.

The difference between the two treatment groups will be tested using the Fisher's Exact Test. This test will be conducted with the type I (α) error of 0.05 for statistical significance (2-tailed). In addition, a Kaplan-Meier plots will be generated for time to death for each treatment group.

INVESTIGATOR AGREEMENT

Protocol INOT22
Version: Amendment I

I have read the protocol, "Comparison of Supplemental Oxygen and Nitric Oxide for Inhalation Plus Oxygen in the Evaluation of the Reactivity of the Pulmonary Vasculature During Acute Pulmonary Vasodilator Testing", Protocol INOT22 (version 1), and agree to conduct the study as outlined therein. I will make a reasonable effort to conduct the study in a timely and efficient manner and will ensure that all participating staff members are adequately trained to carry out the tasks for which they have been assigned.

I will submit this protocol and all other pertinent information to my IRB/IEC for approval.

_____ _____
Principal Investigator's Signature Date

_____
Name of investigator (printed)

APPENDIX 2

[redacted]

From: Macrae Duncan [mailto:D.Macrae@rbh.nthames.nhs.uk]
Sent: [redacted]
To: James Baldassarre; david.wessel@cardio1.tch.harvard.edu; rjb3@columbia.edu; Mary.Mullen@CARDIO.CHBOSTON.ORG
Cc: Sara.Skinner@inveresk.com; Jodee A. Newman; Sandra.Cottrell@inotherapy.com; Richard Straube
Subject: RE: follow up from teleconference

Dear All,

Sorry to have been unable to make the conference due to an unexpected clinical event.

I can concur with the conclusions circulated. There is an issue around awakening / recovery from anaesthesia in these very fragile patients. If the wrong decisions are made they will rapidly decompensate.

Duncan

-----Original Message-----
From: james.baldassarre@inotherapy.com [mailto:james.baldassarre@inotherapy.com]
Sent: [redacted]
To: david.wessel@cardio1.tch.harvard.edu; rjb3@columbia.edu; Macrae Duncan; Mary.Mullen@CARDIO.CHBOSTON.ORG
Cc: Sara.Skinner@inveresk.com; jodee.newman@inotherapy.com; Sandra.Cottrell@inotherapy.com; richard.straube@inotherapy.com
Subject: follow up from teleconference

Dear all,

just to summarize and ask for confirmation:

1) The number of SAEs is very surprising. In the collective experience of Columbia and Boston Childrens (nearly 2000 procedures) cardio-respiratory arrest is exceedingly rare. Some of the events may be due to the relative inexperience of the operators, and the use of general anaesthesia. Use of NO *perse* doesn't seem to be the major concern. Any investigators added to the trial should be very well experienced.

2) There is a reconized concern that inhaled NO may raise the wedge in patients with diastolic dysfunction, and the clinical sequelae are likely to be most serious in those with an elevated PCWP at baseline (e.g. >/= 20 mmHg). It may be prudent to exclude from the study any child with an elevated baseline PCWP.

3) Cardiomyopathy need not be excluded, given the restriction on baseline wedge pressure

4) Separately from these issues, we propose that kids on bosanten or CCBs may be enrolled in the study. (No change need to the protocol)

5) When we have agreement on these issues, the protocol will be amended.

6) Final note: Jim Baldassarre to meet with Dr Barst re: longer term follow up of kids in this study.

Dr James S. Baldassarre
Sr Director, Clinical Research
INO Therapeutics LLC
O: 908-238-6363
C: 908-500-8111

APPENDIX 3

TITLE:	**Comparison of Supplemental Oxygen and Nitric Oxide for Inhalation Plus Oxygen in the Evaluation of the Reactivity of the Pulmonary Vasculature During Acute Pulmonary Vasodilator Testing**
DRUG:	INOmax® (nitric oxide) for inhalation
INDICATION:	Diagnostic Use
SPONSOR:	INO Therapeutics 6 Route 173 Clinton, NJ 08809
PROTOCOL:	INOT22
DRUG DEVELOPMENT PHASE:	Phase 3
VERSION:	Amendment II
DOCUMENT DATE:	[redacted]
STUDY INITIATION:	
STUDY DURATION:	2 years
MEDICAL MONITOR:	James S. Baldassarre, MD Senior Director of Research & Development Phone (908) 238-6363 Fax (908) 238-6634
REGULATORY CONTACT:	Sandra Cottrell VP-Global Regulatory Affairs Mary Ellen Zamstein U.S. & Canadian Regulatory Affairs
STUDY CONTACT:	Jodee Newman, RN Project Leader Phone (908) 238-6317 Fax (908) 238-6634
GCP:	These studies will be performed in compliance with good clinical practices (GCP) guidelines. All essential documents will be archived.

2. SYNOPSIS

Sponsor: INO Therapeutics, LLC	
Name of Finished Product: INOmax® (nitric oxide) for inhalation	
Name of Active Ingredient: Nitric Oxide for Inhalation	
Protocol Number: INOT22	
Title of Study: Comparison of Supplemental Oxygen and Nitric Oxide for Inhalation Plus Oxygen in the Evaluation of the Reactivity of the Pulmonary Vasculature During Acute Pulmonary Vasodilator Testing	
Investigators: Pr. Daniel Sidi, Dr. Alain Fraisse, Dr. Federico Larraya, Dr. Jose Luis Zunzunegui, Dr. Joaquin Jose Bartrons, Prof. Dr. Rolf Berger, Dr. Alan Magee, Dr. Mary Mullen, Dr. Robyn Barst, et al. TBD	
Study Centers: Hopital Necker, Paris, France; CHU la Timone-Hopital d'enfants, Marseille, France; Hospital Materno-Infantil XII de Octubre, Madrid, Spain; Hospital Gregorio Maranon, Madrid Spain; Hospital Sant Joan de Deu, Barcelona, Spain; Beatrix Children's Hospital, Univ. Hospital Groningen, Amsterdam, Netherlands; The Royal Brompton Hospital, London, UK; Boston Children's Hospital, Boston, MA, US; Columbia Presbyterian Hosptital, New York, NY, US, et al. TBD	
Study Period: [redacted]	**Phase of development:** III
Objectives: Compare utility and side effects of oxygen versus nitric oxide for inhalation plus oxygen in determining pulmonary vasoreactivity.	
Methodology: An open, prospective, randomized, multi-center, controlled diagnostic trial.	
Number of patients planned: Enrollment will proceed until at least 25 patients per entry diagnosis and at least 150 patients have been enrolled.	
Anticipated duration of trial: 2 years	

Diagnosis and main criteria for inclusion: Patients between the ages of 4 weeks and eighteen years undergoing diagnostic right heart catheterization scheduled to include acute pulmonary vasodilation testing to assess pulmonary vasoreactivity. The expected population will be patients with:

1) Idiopathic Pulmonary Arterial Hypertension
2) Congenital heart disease with pulmonary hypertension;
3) Cardiomyopathies;

Patients who are either under general anesthesia or awake sedation will be included in this protocol. Patients will be stratified based on entry diagnosis.

Test product, dose and mode of administration: Nitric oxide for inhalation 800 ppm, administered at a dose of 80 ppm, nitric oxide for inhalation plus 100% O_2 and 100% O_2, via facemask or endotracheal tube.

Duration of treatment: 10 minutes of nitric oxide for inhalation at 80 ppm and 10 minutes of 80 ppm nitric oxide for inhalation plus 100% O_2, and 10 minutes of 100% O_2; delivered via facemask or endotracheal tube.

Criteria for evaluation:

Primary endpoint:

Number of patients receiving a combination of NO and O_2 versus the number of patients receiving O_2 alone that meet response criteria. The response criteria are as follows:

Patients with Idiopathic Pulmonary Arterial Hypertension or patients with CHD who do not have an unrestricted shunt at the level of the ventricle or ductus arteriosus, response will be defined as:

1) a decrease in PAPm $\geq$ 20% and no decrease in cardiac index (within 5%)

Patients with cardiomyopathy or patients with CHD who have an unrestricted shunt at the level of the ventricle or ductus arteriosus, response will be defined as:

1) a decrease in PAPm $\geq$ 20% and no decrease in cardiac index (within 5%)

or

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

Secondary endpoints:

1) Number of patients receiving NO versus the number of patients receiving O_2 that meet response criteria, as defined above.
2) Number of patients receiving a combination of NO and O_2 versus the number of

patients receiving NO alone that meet response criteria, as defined above.

3) PVRI, PAPm and Cardiac Index readings in Room Air versus NO alone, O_2 alone and the combination of NO and O_2
4) Change in the ratio of PAPm to SAPm by treatment
5) Survival at 1 year and 3 years by response

Safety endpoints:

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

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

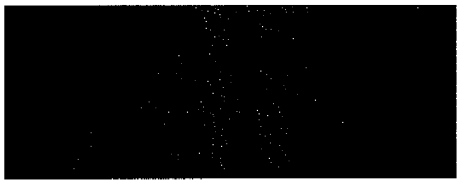
It is agreed that, for reasonable cause, either the investigator or the sponsor, INO Therapeutics, LLC may terminate this study, provided written notice is submitted at a reasonable time in advance of intended termination.

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

or

2) a decrease in PVRI ≥ 25% and no decrease in cardiac index (within 5%)

These variables will be calculated as follows:

% Change in PAPm from Baseline =

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

% Change in PVRI from Baseline =

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

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

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

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

The alternative hypothesis is:

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

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

D. Secondary Efficacy Analysis

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

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

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

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

The alternative hypothesis is:

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

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

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

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

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

The alternative hypothesis is:

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

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

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

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

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

The alternative hypothesis is:

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

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

The alternative hypothesis is:

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

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

The alternative hypothesis is:

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

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

The alternative hypothesis is:

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

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

The alternative hypothesis is:

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

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

The alternative hypothesis is:

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

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

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

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

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

Change in the Ratio of PA Pressure to Systemic Pressure

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

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

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

Survival at 1 and 3 Years Following the Diagnostic Procedure

It is hypothesized that there is a difference in rates of survival at 1 and 3 years of those who met response criteria as outlined in section C of this analytic plan. The hypotheses are formerly expressed as:

H_o: There is no difference in the survival rate of patients with a positive response in PAPm or PVRI between the NO and O_2 group versus the O_2 alone group.
The alternative hypothesis is:
H_a: A difference exists in the survival rate of patients with a positive response in PAPm or PVRI between the NO and O_2 group versus the O_2 alone group.

The difference between the two treatment groups will be tested using the Fisher's Exact Test. This test will be conducted with the type I (α) error of 0.05 for statistical significance (2-tailed). In addition, a Kaplan-Meier plots will be generated for time to death for each treatment group.

E. Safety Analysis

Serious Adverse Events

The analysis will be performed on the number and types of serious adverse events reported in each treatment group. The incidence of all serious adverse events, stratified by MEDRA terms, MEDRA body system, and patients with specific serious adverse events will be tabulated. Additionally, the serious adverse events will be stratified by age, sex and race.

H_o: There is no difference in the number of reported serious adverse events between the NO, NO + O_2 and O_2 alone groups.

H_a: A difference exists in the number of reported serious adverse events between the NO, NO + O_2 and O_2 alone groups.

This comparison will be made using Cochran's Test for Related Observations.

Drug Related Adverse Events

The analysis will be performed on the number and types of drug related adverse events reported in each treatment group. The incidence of all drug related adverse events, stratified by MEDRA terms, MEDRA body system, and patients with specific adverse events will be tabulated. Additionally, the adverse events will be stratified by age, sex and race.

H_o: There is no difference in the number of reported drug related adverse events between the NO, NO + O_2 and O_2 alone groups.

H_a: A difference exists in the number of reported drug related adverse events between the NO, NO + O_2 and O_2 alone groups.

This comparison will be made using Cochran's Test for Related Observations.

F. Additional Analyses

All primary methods of analysis have been previously outlined in this document. However, INO Therapeutics reserves the right to perform any additional analyses deemed necessary according to any of the following reasons:

1. Any steering committee or medical monitor recommendations based on investigator concerns.
2. The presence of maldistributed baseline characteristics.
3. The administration of any medications thought to be affecting the treatment as determined by the steering committee and/or the medical monitor.

Additionally, several exploratory analyses will be conducted to determine the existence of any possible relationships between the response variables and diagnosis, delivery system, demographic criteria, etc. Due to the unknown nature of these analyses, INO Therapeutics, LLC declines to formalize the testing procedures in this analytic plan.

G. Interim Analyses

No interim analysis for efficacy or safety in this study is planned.

APPENDIX 3. LISTING OF AMENDMENT 1 CHANGES

AMENDMENT 1 CHANGES:

Cover Page, Version

Changed From:

"Original Protocol"

Changed To:

"Amendment 1"

Cover Page, Document Date

Changed From:

[redacted]

Changed To:

[redacted]

Cover Page, Study Contact

Deleted: Paul Bridges, European Regulatory Affairs

Changed From:

"Rebecca Light, Clinical Research Manager"

Changed To:

"Jodee Newman, Project Leader"

Synopsis

Changed From:
"Sponsor-INO Therapeutics, Inc."

Changed To:
"Sponsor-INO Therapeutics, LLC"

Changed From:
"Investigators-TBD"

Changed To:
"Investigators- Pr. Daniel Sidi,, Dr. Alain Fraisse, Dr. Federico Larraya, Dr. Jose Luis Zunzunegui, Dr. Joaquin Jose Bartrons, Prof. Dr. Rolf Berger, Dr. Alan Magee, Dr. Mary Mullen, Dr. Robyn Barst "

Changed From:
"Study Centers-TBD"

Changed To:
Study Centers-Hopital Necker, Paris, France; CHU la Timone-Hopital d'enfants, Marseille, France; Hospital Materno-Infantil XII de Octubre, Madrid, Spain; Hospital Gregorio Maranon, Madrid Spain; Hospital Sant Joan de Deu, Barcelona, Spain; Beatrix Children's Hospital, Univ. Hospital Groningen, Amsterdam, Netherlands; The Royal Brompton Hospital, London, UK; Boston Children's Hospital, Boston, MA, US; Columbia Presbyterian Hosptital, New York, NY, US

Secondary Endpoints-Addition:

4) Change in the ratio of PAPm to SAPm by treatment

5) Survival at 1 year by response

4. List of Abbreviations and Definitions of Terms

Addition:
Mean Systolic Arterial blood pressure

Page 19 Section 9.1

Addition:
"Following the acute diagnostic procedure, a brief follow up contact will be made on each patient to determine the vital status 1 year after the diagnostic procedure."

Section 9.5.1 Table 1 - Footnote

Addition:
Assessment-Baseline :Arterial pH
Follow up assessment at 1 yr. Will consist of telephone call to assess medical therapies or surgical procedures pertaining to pulmonary/cardiac disease, and vital status /date of death if applicable.

9.5.2 Data Collection

Addition:
Of Arterial pH to-

Baseline Measurement ***and*** *Measurements Following Third Treatment Administration*

Measurements 1 year after the diagnostic procedure

- Therapies received since the diagnostic procedure
- Date of surgery (if any)
- Vital status and date of death, if applicable

9.5.5 Efficacy Variables

Secondary Endpoints-Addition:

4) Change in the ratio of PAPm to SAPm by treatment

5) Survival at 1 year by response

10.4.2 Serious Adverse Events

Changed From:

Any serious adverse event must be reported to INO Therapeutics within 24 hours by telephone to:

Catherine Evans, Regulatory Affairs Associate

Phone: (908) 238-6655

Fax: (908) 238-6635

Dr. James S. Baldassarre

Phone: (908) 238-6363 Cell: (908) 500-8111

Changed To:

All serious adverse events occurring during the study, and within 12 hours of the discontinuation of treatment gas, or hospital discharge whichever comes first, must be reported within 24 hours to INO Therapeutics by fax/telephone to:

Catherine Evans

INO Therapeutics Regulatory Affairs Associate

Phone: + 001 908 238-6655

Fax: +001 908 238-6635

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

Dr. James S. Baldassarre

INO Therapeutics Senior Director Research & Development

Phone: +001 908 238-6363

Cell: +001 908 500-8111

Added to text: *"within 24 hours by completing an SAE packet with"*

Delete page 40, second to last paragraph:

All patient/subject deaths will be reported independent of the temporal relationship to the patient's/subject's study participation and treatment (i.e. test drug, placebo).

Appendix 2. Analytic Plan

Section D-page 46/47 Addition:

Change in the Ratio of PA Pressure to Systemic Pressure

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

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

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

Survival at 1 Year Following the Diagnostic Procedure

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

H_o: There is no difference in the survival rate of patients with a positive response in PAPm or PVRI between the NO and O_2 group versus the O_2 alone group.
The alternative hypothesis is:
H_a: A difference exists in the survival rate of patients with a positive response in PAPm or PVRI between the NO and O_2 group versus the O_2 alone group.

The difference between the two treatment groups will be tested using the Fisher's Exact Test. This test will be conducted with the type I (α) error of 0.05 for statistical significance (2-tailed). In addition, a Kaplan-Meier plots will be generated for time to death for each treatment group.

APPENDIX 4. LISTING OF AMENDMENT II CHANGES

AMENDMENT II CHANGES:

Cover Page, Version

Changed From:

"Amendment I"

Changed To:

"Amendment II"

Cover Page, Document Date

Changed From:

[redacted]

Changed To:

[redacted]

Cover Page, Duration

Changed From:

"1½ years"

Changed To:

"2 years"

Cover Page, Study Contact

Addition:

Sandra Cottrell
VP Global Regulatory Affairs

Synopsis

Investigators

Addition:
et al. TBD

Study Centers

Addition:
et al. TBD

Study Period

Anticipated Completion:

Changed From:

[redacted]

Changed To:

[redacted]

Anticipated duration of trial

Changed From:

1½ years

Changed To:

2 years

Criteria for Evaluation

Secondary Endpoints:

Changed From:

5) Survival at 1 year by response

Changed To:

5) Survival at 1 year and 3 years by response

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

Changed To:
Approximately 18 sites will participate in the trial with an expected total enrollment of a minimum of 150 patients (approximately 9 patients per site).

9.3.2Exlusion Criteria

Addition:

5) Baseline PCWP > 20 mmHg

9.4.2 Identity of Investigational Product

Changed From:
Nitric oxide for inhalation will be supplied in size "88", aluminum cylinders at a concentration of 800 ppm, balance nitrogen (99.92% grade 5 nitrogen, 0.08% pharmaceutical grade nitric oxide).

Changed To:

Nitric oxide for inhalation will be supplied in size "88" US or "10L" EU, aluminum cylinders at a concentration of 800 ppm, balance nitrogen (99.92% grade 5 nitrogen, 0.08% pharmaceutical grade nitric oxide).

9.5 Table 1

Addition to table:

pH- following third treatment administration

Addition to Footnote:

3 year follow up

9.5.2 Data Collection

Changed From:

Measurements 1 year after the diagnostic procedure

Changed To:

Measurements 1 year and 3 years after the diagnostic procedure

9.5.5 Efficacy Variables

Secondary Endpoints

Changed From:

Survival at 1 year by response

Changed To:

Survival at 1 year and 3 years, by response

9.7.1 Sample Size Determination

Changed From:

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

Changed To:

Enrollment will proceed until at least 150 patients have been enrolled in the trial.

Throughout document:

Changed From:

INO Therapeutics, Inc.

Changed To:

INO Therapeutics, LLC

Appendix 2. Analytic Plan -D. Secondary Efficacy Analysis

Changed From:

Survival at 1 Year Following the Diagnostic Procedure

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

Survival at 1 and 3 Years Following the Diagnostic Procedure

It is hypothesized that there is a difference in rates of survival at 1 and 3 years of those who met response criteria as outlined in section C of this analytic plan.

Appendix 3. Amendment I Changes

Section 9.1

Changed From:

Page 14

Changed To:

Page 19

Appendix 2. Analytic Plan Section D

Changed From:

Page 42/43

Changed To:

Page 46/47

Secondary Endpoints:

Point #5 corrected from #6.

INVESTIGATOR AGREEMENT

Protocol INOT22
Version: Amendment II

I have read the protocol, "Comparison of Supplemental Oxygen and Nitric Oxide for Inhalation Plus Oxygen in the Evaluation of the Reactivity of the Pulmonary Vasculature During Acute Pulmonary Vasodilator Testing", Protocol INOT22 (version 1), and agree to conduct the study as outlined therein. I will make a reasonable effort to conduct the study in a timely and efficient manner and will ensure that all participating staff members are adequately trained to carry out the tasks for which they have been assigned.

I will submit this protocol and all other pertinent information to my IRB/IEC for approval.

_____ _____
Principal Investigator's Signature Date

_____
Name of investigator (printed)

APPENDIX 4

6 Route 173, Clinton, NJ 08809
Tel (908) 238-6600 Fax (908) 238-6633
http://www.inotherapeutics.com

[redacted]

Center for Drug Evaluation and Research
Office for Drug Evaluation I
Division of Cardio-Renal Drug Products
(HFD-110)
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

IND 63,096
INOmax® (nitric oxide) for inhalation

Serial No.: 091

Protocol Amendment
Change in Protocol
New Investigator: Updated Investigator Information

Dear Sir or Madam:

Reference is made to Investigational New Drug Application 63,096 for the treatment of cardiopulmonary disease and sickle cell disease. At this time we wish to provide amendments to protocols INOT22 and INOT43. Also, we wish to provide new investigator information and an amendment to protocol INOT41 and new investigator information for INOT36.

Protocol INOT22
Comparison of Supplemental Oxygen and Nitric Oxide for Inhalation Plus Oxygenation in the Evaluation of the Reactivity of the Pulmonary Vasculature During Acute Pulmonary Vasodilator Testing. (Originally submitted [redacted] Serial No. 071 and amended [redacted] Serial No. 083)

Below is a list of major changes incorporated into protocol INOT22, Amendment 2.

- Anticipated duration of trial changed from 1 ½ to 2 years.
- Revised investigator sites information from approximately 8 sites with approximately 20 patients per site to approximately 18 sites with approximately 9 patients per site.
- Revised exclusion criteria to add Baseline PCWP> 20 mmHg.
- Revised data collection from 1 year after the diagnostic procedure to 1 year and 3 years after the diagnostic procedure.
- Revised sample size determination from "the minimum number of patients required per entry diagnosis is 25. Enrollment will proceed until at least 25 patients per entry

diagnosis are enrolled and there are at least 150 patients in the trial" to "Enrollment will proceed until at least 150 patients have been enrolled in the trial."

- Appendix 2. Analytic Plan –D. Secondary Efficacy Analysis changed from 1 year to 1 and 3 years.

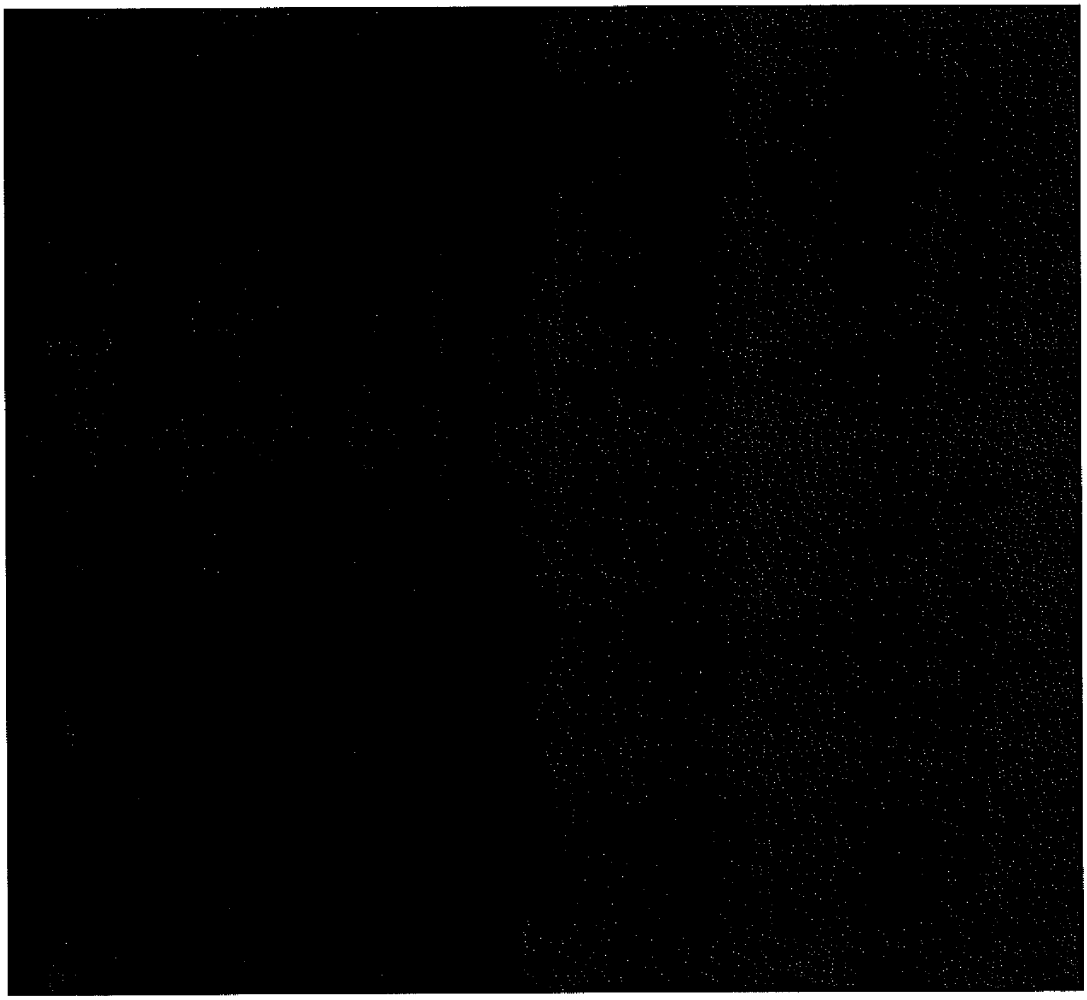
For ease of review, a detailed list of all revisions to this amended protocol is included in appendix 4 of the appended protocol.

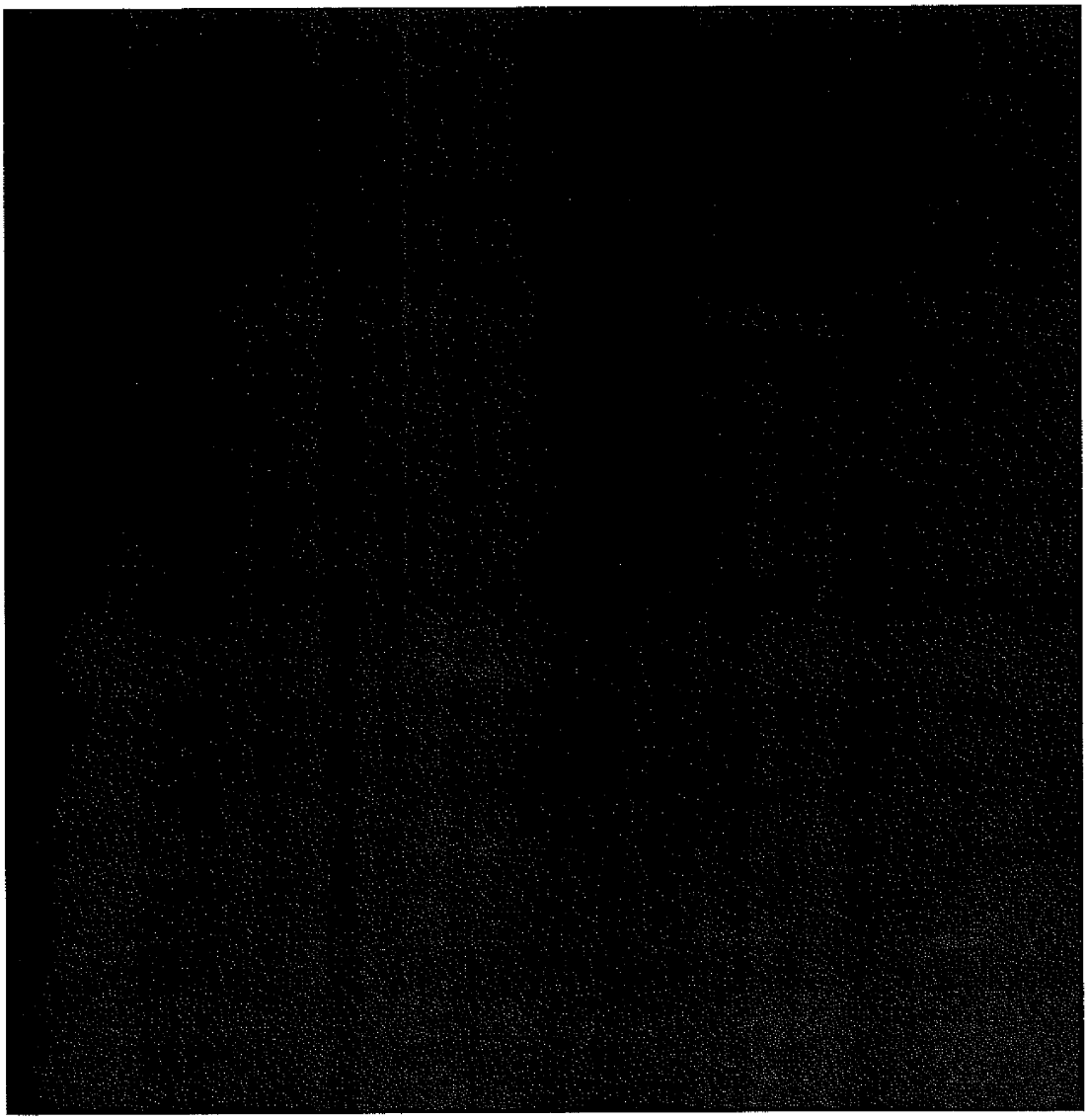
Prior to enrollment of subjects under Amendment 2, further revisions were made to the protocol resulting in Amendment 3.

Below is a list of major changes incorporated into protocol INOT22, Amendment 3.

- Revised sample size information from 150 patients to 100 patients.

For ease of review, a detailed list of all revisions to this amended protocol is included in appendix 5 of the appended protocol.





Should you have any questions and/or comments, please contact me directly at 908-238-6337.

Sincerely,

INO Therapeutics,

Mary Ellen Zamstein

Mary Ellen Zamstein
Director, Regulatory Affairs

F: Regulatory IND 63,096 Protocol Amendments [redacted] FDA letter.doc

APPENDIX 5

[redacted]

From: Debra A. Rimar
Sent: [redacted]
To: James Baldassarre
Subject: FW: INOT22 - latest draft CSR (v.0.3)

Sorry.

Debra Rimar
INO Therapeutics/IKARIA
6 Route 173
Clinton, NJ 08809
debra.rimar@ikaria.com
908.238.6322

From: James Baldassarre
Sent: [redacted]
To: Debra A. Rimar
Subject: RE: INOT22 - latest draft CSR (v.0.3)

There's no attachment.

jim

From: Debra A. Rimar
Sent: [redacted]
To: James Baldassarre
Subject: INOT22 - latest draft CSR (v.0.3)
Importance: High

Jim:

Latest version w/inclusion of two recent tables + new pvri Figure 5 + various minor changes.

See highlighted areas needing possible attention.

Jodee taking Safety section.

Make changes directly in the doct. and return and I will merge into master.

Debra Rimar
INO Therapeutics/IKARIA
6 Route 173

Clinton, NJ 08809
debra.rimar@ikaria.com
908.238.6322

NITRIC OXIDE FOR INHALATION, INOmax®

INOT22

COMPARISON OF SUPPLEMENTAL OXYGEN AND NITRIC OXIDE FOR INHALATION PLUS OXYGEN IN THE EVALUATION OF THE REACTIVITY OF THE PULMONARY VASCULATURE DURING ACUTE PULMONARY VASODILATOR TESTING

Indication studied:	*Diagnostic use*
Developmental phase of study:	*PHASE 3*
First patient enrolled:	*<<Date>>*
Last patient completed:	*<<Date>>*
Release date of report:	*<<Date>>*

Company/Sponsor signatory: *<<Name>>*
<<Telephone Number>>
<<Fax Number>>

This trial was conducted in accordance with the ethical principles of Good Clinical Practice (GCP), according to the International Conference on Harmonisation (ICH) Harmonized Tripartite Guideline.

Sponsor's Responsible Medical Officer <<Signature, Date>>

3. TABLE OF CONTENTS FOR THE INDIVIDUAL CLINICAL STUDY REPORT

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and specialist terms are used in this study report.

Table 1: Abbreviations and Specialist Terms

Abbreviation or specialist term	Explanation
AE	Adverse event
APVT	Acute pulmonary vasodilator testing
CFR	Code of federal regulations
CHD	Congenital heart disease
CI	Cardiac index
CO	Cardiac output
CRA	Clinical research associate
CRF	Case report form
CVPm	Mean central venous pressure
DAP	Diastolic arterial blood pressure
FDA	Food and Drug Administration
GCP	Good Clinical Practice
Hgb	Hemoglobin
HR	Heart rate
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IPAH	Idiopathic pulmonary hypertension
IRB	Institutional Review Board
MAP	Mean arterial pressure
mm Hg	Millimeters of mercury
n	Total number of patients (sample size)
NO	Nitric oxide
NO_2	Nitrogen dioxide
O_2	Oxygen
PAP	Pulmonary arterial pressure

Abbreviation or specialist term	Explanation
PAPm	Mean pulmonary arterial pressure
PAPs	Systolic pulmonary arterial pressure
PAWPm	Mean pulmonary artery wedge pressure
PCWP	Pulmonary capillary wedge pressure
PDE5	Phosphodiesterase type 5
PH	Pulmonary hypertension
ppm	Parts per million by volume (40 pm = 0.004% of the inhaled gas)
PVR	Pulmonary vascular resistance
PVRI	Pulmonary vascular resistance index
SAE	Serious adverse event
SAP	Systolic arterial blood pressure
SAPm	Mean systolic arterial blood pressure

5. ETHICS

5.1. Independent Ethics Committee (IEC) or Institutional Review Board (IRB)

The protocols and local Informed Consent Forms were reviewed and approved by each of the participating institution's IRB/IEC prior to the initiation of patient accrual. The IRB/IEC was notified of all protocol amendments. In addition, progress reports were submitted to the IRB/IEC by the investigator as indicated by the IRB/IEC's guidelines. Each IRB/IEC met the Food and Drug Administration's (FDA) and/or International Conference on Harmonization (ICH) requirements for composition, documentation, and operational procedures. A list of all IECs and IRBs is provided in Appendix 16.1.3 along with the name of the committee chair.

5.2. Ethical Conduct of the Study

This trial was designed and monitored in accordance with INO Therapeutics LLC procedures, which comply with the ethical principles of Good Clinical Practices (GCP) as required by the major regulatory authorities, and in accordance with the Declaration of Helsinki.

5.3. Patient Information and Consent

All patients (or legally authorized representative) provided informed written consent after having had adequate time to consider their participation in the study. Consent was obtained prior to any protocol-related procedures that were not part of the patient's normal care. Written documentation of consent was recorded on a signature page and the patient or their legal representative received a copy of the consent form according to ICH GCP guidelines. A sample of the consent form is provided in Appendix 16.1.3.

6. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

A total of 19 sites participated in the trial with a total enrollment of 136 patients. A listing of principal investigators at each study site and their institutional affiliations is provided in Appendix 16.1.4. Signatures of principal investigators are provided in Appendix 16.1.5.

The study was initiated by INO Therapeutics LLC and a Steering Committee was established to review the contents of the protocol and subsequent amendments, monitor the progress of the trial, and provide recommendations to the sponsors on changes in the procedures and conduct of the trial. Steering Committee members included:

- David Wessel, MD, Boston Children's Hospital, Boston, MA, USA.
- Robyn Barst, MD, Columbia Presbyterian Hospital, New York, NY, USA.
- Duncan Macrae, MD, Royal Brompton Hospital, London, UK.

Due to the short duration of the study, the fact that the treatment assignments were not blinded and the fact that the study endpoints were not serious irreversible events, no Data Safety Monitoring Board was established and no interim analysis of efficacy was carried out. To ensure the well-being of patients enrolled in the trial, safety was monitored on an ongoing basis. All adverse events (AEs) and serious AEs (SAEs) were reviewed by the Steering Committee on a regular basis and reported to the appropriate health authorities and IRBs/IECs as per ICH GCP and as required by local regulations.

7. INTRODUCTION

Pulmonary hypertension (PH) is a condition characterized by elevated pulmonary artery pressures. Pulmonary hypertension may be idiopathic (i.e., without an identified cause) or secondary to other disease processes (e.g., intrinsic heart or lung disease, collagen-vascular disease, toxins or infections).[1,2] In either case, it is associated with changes in the pulmonary vascular bed such as vasoconstriction, vascular-wall remodeling, and thrombosis *in situ* resulting in increased vascular resistance.[2] Abnormal production of vasorelaxants and vasoconstrictors by the pulmonary endothelium may also play a role. Endothelium-derived metabolite imbalances of the vasorelaxant prostacyclin and vasoconstrictor thromboxane have been linked to PH, as have impaired synthesis of the vasorelaxant nitric oxide (NO) and enhanced production of vasoconstrictor endothelin.[2-5] Conventional medical treatments consisting of vasodilators, inotropes, anticoagulants, diuretics or oxygen (O_2) are aimed at decreasing mean pulmonary arterial pressure (PAPm) and pulmonary vascular resistance (PVR). In patients with primary PH and symptomatic right ventricular failure, the median survival time is less than 3 years, and surgical intervention such as heart or heart/lung transplantation may have to be considered.[2,6]

For patients with right ventricular failure and lung disorders, the prognosis and course of treatment are determined by acute pulmonary vasodilation testing (APVT). A reduction in PAPm and PVR with acute vasodilator treatment may be used to predict therapeutic efficacy of long-term vasodilator medication. APVT is also used to evaluate patients being considered for heart or heart/lung transplantation; elevated pulmonary artery pressures and PVR place a strain on the right ventricle, leading to an increased risk of perioperative morbidity and mortality due to right heart failure post-heart transplant.[7-10]

Administration of 100% supplemental O_2 has been a standard in APVT, especially in pediatric patients. However, some patients with reactive pulmonary vasculature fail to respond to acute treatment with 100% supplemental O_2. Nitric oxide has been shown to be selective for the pulmonary versus the systemic vasculature, and it does not increase pulmonary shunting.[11] It has been shown that combination testing with inhaled NO and O_2 provides additional pulmonary vasodilation in patients with a reactive vascular bed, and NO plus O_2 is more effective than O_2 alone when used as a pulmonary vasodilator.[10,11]

INOmax® (Nitric oxide for inhalation) is approved by the FDA for use in term newborns with PH and hypoxic respiratory failure in conjunction with mechanical ventilation and other supportive measures to allow more blood to circulate in the lung, which helps to increase blood O_2 levels.[12] Nitric oxide, the endothelial-derived relaxing factor, is a major physiologic regulator of endothelial smooth muscle tone. In published studies, NO for inhalation has been shown to reduce pulmonary artery pressures in patients with adult respiratory distress syndrome, chronic obstructive lung disease, PH, and congenital heart disease (CHD).[7,8,10,13] Studies in primary and secondary forms of PH have shown that short-term NO for inhalation can selectively reduce both PAPm and PVR with minimal side effects.[7,10] Nitric oxide for inhalation has a short half-life, as it quickly binds to hemoglobin (Hgb) within the pulmonary capillary lumen to form methemoglobin,

rendering it inactive, and systemic vasodilation effects with NO are minimal. Potential risks of NO are rebound PH, increased nitrogen dioxide (NO_2, a lung irritant), and methemoglobinemia. However, due to the short duration of NO delivery in this study, it is unlikely these events would occur.

This study tests the hypothesis that a combination of inhaled NO and O_2 is more sensitive than 100% supplemental O_2 alone in detecting pulmonary vasoreactivity in patients with PH.

This report is intended to report only the primary endpoint and other short-term endpoints. The results of 1- and 3-year follow-up will be reported in subsequent reports, as data becomes available.

8. STUDY OBJECTIVES

The primary objective of the trial was to compare the number of patients with reversible PH (vasoreactivity) due to NO for inhalation and O_2 as compared to 100% O_2. The criteria for response were:

- Patients with idiopathic pulmonary arterial hypertension (IPAH) or patients with CHD who did not have an unrestricted shunt at the level of the ventricle or ductus arteriosus: a decrease in PAPm ≥ 20% and no decrease in cardiac index (CI) (within 5%).
- Patients with cardiomyopathy or patients with CHD who had an unrestricted shunt at the level of the ventricle or ductus arteriosus: a decrease in PAPm ≥ 20% and no decrease in CI (within 5%) or a decrease in PVR index (PVRI) ≥ 25% and no decrease in CI (within 5%).

Additional study objectives were to compare the incidence and types of drug-related AEs and SAEs, as well as the number of patients with reversible PH due to NO for inhalation alone compared to 100% O_2 and to O_2 with NO for inhalation.

9. INVESTIGATIONAL PLAN

9.1. Overall Study Design and Plan: Description

This trial followed an open, prospective, multicenter, randomized controlled design and compared the utility and side effects of O_2, NO, and the combination of NO and O_2 in determining pulmonary reactivity. Each patient was screened for enrollment and fulfilled all entry criteria described in Section 9.3. Upon obtaining informed consent approved by the institution's IRB/IEC, patients were randomly assigned, using a randomization table, to receive either NO for inhalation at 80 parts per million (ppm) or 100% O_2 as their initial dose. Patients were either under general anesthesia or awake sedation. Once the study drug delivery equipment was prepared, baseline data were collected. Using a calibrated INOvent®, either NO for inhalation at 80 ppm or 100% O_2 was continuously administered to the patient for 10 minutes followed by data collection. The second dose was the same as the first dose with the addition of either 80 ppm NO for patients receiving O_2, or 100% O_2 for patients receiving NO. This dose of 80 ppm NO and 100% O_2 was delivered for 10 minutes followed by data collection. There was a 10 minute washout period following this administration. Baseline data were again collected followed by a 10 minute administration of either 80 ppm NO or 100% O_2. The study drug delivered for this third administration was not randomly assigned for the initial study drug administration.

For each patient, NO_2 levels were monitored throughout the treatment period. Treatment with study gas was discontinued if NO_2 levels exceeded 3 ppm. Treatment could also be discontinued at the discretion of the attending physician or following the occurrence of an adverse response to study drug. All AEs were recorded while on study gas. Serious AEs were recorded during the treatment period through Day 1 or discharge from the hospital, whichever came first. Qualification and reporting of all SAEs was carried out as per the Code of Federal Regulations (CFR) and ICH guidelines.

Following the acute diagnostic procedure, a brief follow-up contact was to be made for each patient to determine vital status 1 and 3 years after the study procedure.

9.2. Discussion of the Study Design, Including the Choice of Control Groups

This was an open, randomized, prospective, multicenter, controlled trial designed to demonstrate which diagnostic treatment was most capable of identifying patients with a reactive pulmonary vascular bed. Each patient served as his or her own control and received all three treatment regimens: 80 ppm NO for inhalation, 80 ppm NO and 100% O_2, and the comparison treatment, 100% O_2. Due to the short half-life of NO, a 10 minute washout period following the NO for inhalation and 100% O_2 treatment allowed sufficient time for elimination of the drug effect before administration of the comparison treatment. Only a single study phase without O_2 was included in this trial. This approach

was taken because an additional treatment period without O_2 would have been potentially unsafe for the unstable patients included in this study.

9.3. Selection of Study Population

The patients enrolled in this study had IPAH, CHD (with or without intravascular shunt) with PH, and cardiomyopathies. Patients were stratified based on entry diagnosis and included those who were awake or under general anesthesia. However, after the first 45 patients were enrolled, the protocol was amended such that patients with PCWP > 20 mm Hg were excluded. This was done at the suggestion of the Steering Committee due to the potential risk in that subgroup. The total sample size was reduced from 150 to 100 patients.

9.3.1. Inclusion Criteria

For inclusion into the trial, patients were required to fulfill all of the following criteria:

- Male or female 4 weeks to 18 years of age (inclusive)

  Idiopathic Pulmonary Arterial Hypertension (PAPm >25 mm Hg at rest, pulmonary capillary wedge pressure [PCWP] ≤ 15 mm Hg, and PVRI > 3W u·m^2, or diagnosed clinically with no previous catheterization)
- Congenital heart disease with PH repaired and unrepaired with PAPm > 25 mm Hg at rest, PVRI >3 Wu·m^2, or diagnosed clinically with no previous catheterization
- Scheduled to undergo right heart catheterization to assess pulmonary vasoreactivity by acute pulmonary vasodilation testing
- Signed IRB/IEC approved consent (an assent if applicable)

9.3.2. Exclusion Criteria

Any of the following was regarded as a criterion for exclusion from the trial:

- Focal pulmonary infiltrates on chest radiograph
- PWCP >20 mm Hg
- Diagnosed with severe obstructive or restrictive pulmonary disease that was significantly contributing to the patient's PH
- Received treatment with NO for inhalation within 30 days prior to study initiation, were on other investigational medications, nitroglycerin, sodium nitroprusside, sildenafil, other phosphodiesterase type 5 (PDE5) inhibitors, or prostacyclin
- Were pregnant (positive urine pregnancy test)

9.3.3. Removal of Patients from Therapy or Assessment

Patients were removed from the trial if any of the following circumstances occurred:

- Study gas was discontinued if NO_2 levels exceeded 3 ppm
- Treatment could also be discontinued if the patient or legal representative withdrew consent or if the investigator deemed it in the best medical interest of the patient

9.4. Treatments

9.4.1. Treatments Administered

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

Patients who were under general anesthesia were intubated and received NO for inhalation, 100% O_2, or a combination of NO and O_2. NO was administered using an INOvent® delivery system through a t-connector downstream of the inspiratory limb of a mechanical ventilator. Patients who were under awake sedation (mild sedation) received NO for inhalation, 100% O_2, or a combination of NO and O_2. The NO was administered using an INOvent® delivery system through a properly fitted, sealed facemask.

Each patient was randomized as to which study drug (80 ppm NO or 100% O_2) they received as the initial dose. The second dose administration was 80 ppm NO for inhalation with 100% O_2 (set - approximate O_2 delivery 90%) and the third dose administration was whichever study drug was not initially administered (NO or 100% O_2). There was a 10 minute washout period between the second and third dose administrations.

9.4.2. Identity of Investigational Products

The active drug, NO for inhalation, was manufactured by INO Therapeutics LLC. Nitric oxide for inhalation was supplied in size "88" US or "10 L" EU aluminum cylinders at a concentration of 800 ppm, balance nitrogen (99.92% grade 5 nitrogen, 0.08% pharmaceutical grade NO). The cylinders were stored in a controlled, limited access area at standard room temperature. Cylinder labels distinguished among sites, but were not pre-assigned patient numbers. The O_2 used in this study was provided by each hospital.

9.4.3. Method of Assigning Patients to Treatment Groups

Randomization of the initial study treatment administered was block randomization by site. Only the first treatment assignment was randomized. The randomization codes were provided to sites in individual envelopes per patient. Patients served as their own controls and received all three treatments.

9.4.4. Selection of Doses in the Study

While varying doses of NO for inhalation have been shown to be safe and effective in decreasing PAPm and PVRI, the use of 80 ppm may elicit a response in a small percentage of nonresponders to lower doses (Wessel D, personal communication, [redacted]). Therefore, 80 ppm of NO for inhalation was used in an effort to capture data from the maximum number of potential responders. Previous studies with NO for inhalation have shown no significant increase in the levels of methemoglobin after very short exposures, even at the dose of 80 ppm.[10,13]

9.4.5. Selection and Timing of Dose for Each Patient

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

9.4.6. Blinding

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

9.4.7. Prior and Concomitant Therapy

Patients who had received treatment with NO for inhalation within 30 days prior to study initiation, other investigational medications, nitroglycerin, sodium nitroprusside, sildenafil or other PDE5 inhibitors, or prostacyclin were excluded from this trial.

Ketamine was not to be used as part of the anesthetic regimen.

Concomitant medications were recorded on the case report form (CRF).

9.4.8. Treatment Compliance

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

9.4.9. Ventilator Weaning and Extubation Strategy

Following the third treatment administration, study patients under general anesthesia were weaned from the mechanical ventilator and extubated according to standard medical care and hospital specific protocol. Study patients under awake sedation had treatments

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

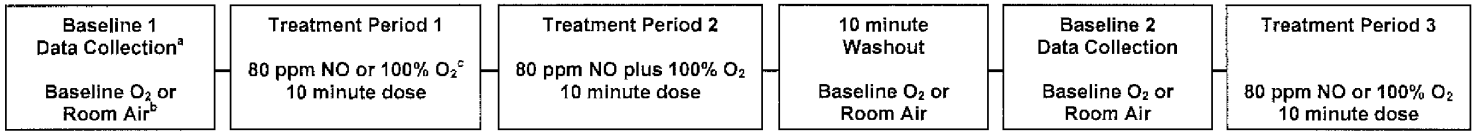
9.5. Efficacy and Safety Variables

9.5.1. Efficacy and Safety Measurements Assessed and Flow Chart

The schedule of assessments is shown in Figure 1 and Table 2. All study procedures were carried out on a single day.

Figure 1: Study Design and Schedule Of Assessments

Data Collection and Treatment



[a] Data collection included hemodynamic measurements and cardiac output (CO)
[b] Baseline measurements were made with room air whenever possible
[c] Patients were randomized as to which treatment would be received first
Follow-up assessments at 1 and 3 years will consist of a brief telephone contact to determine vital status

Table 2: Study Design and Schedule Of Assessments

	Screening	**Baseline** Room air or baseline O_2	**Treatment 1** 80 ppm NO or 100% O_2	**Treatment 2** 80 ppm NO and 100% O_2	**Washout Period**	**Baseline 2**	**Treatment 3** 80 ppm NO or 100% O_2
Informed Consent	X						
Demography		X					
Hgb		X					
Hemodynamic Measurements[a]		X	X	X		X	X
Safety							
AEs[b]			X	X	X	X	X
SAEs[c]			X	X	X	X	X
O_2 consumption		X					
Arterial pH		X					X
Follow-up visit[d]							

[a] Hemodynamic measurements included heart rate (HR), systolic arterial blood pressure (SAP), diastolic arterial blood pressure (DAP), mean arterial pressure (MAP), mean central venous pressure (CVPm), systolic pulmonary arterial pressure (PAPs), diastolic pulmonary arterial pressure (PAPd), PAPm, mean pulmonary artery wedge pressure (PAWPm), and CO.

[b] Adverse events were collected until the patient was discontinued from study gas.

[c] Serious AEs were collected through 12 hours after discontinuation of study gas or discharge, whichever came first. Follow-up assessment at 1 year and 3 years will consist of a telephone call to assess medical therapies or surgical procedures pertaining to pulmonary/cardiac disease, and vital status/date of death if applicable.

[d] Follow-up assessment at 1 and 3 years will consist of a telephone call to assess medical therapies or surgical procedures pertaining to pulmonary/cardiac disease, and vital status/date of death if applicable.

- Baseline measurements included:
  - Compliance with inclusion/exclusion criteria
  - Demographic information and diagnosis (underlying disease)
  - Concomitant medications
  - Hemoglobin (may have been recorded within 1 week of baseline)
  - Hemodynamic parameters: HR, SAP, DAP, MAP, CVPm, PAPs, PAPd, PAPm, PAWPm, and CO (determined by either the Fick or Thermal Dilution method; the method used was recorded in the CRF)
  - Arterial pH
- Measurements following first treatment administration:
  - Hemodynamic parameters: HR, SAP, DAP, MAP, CVPm, PAPs, PAPd, PAPm, PAWPm, and CO
  - Adverse events (until the patient is discontinued from study gas) and SAEs (through study Day 1 or discharge, whichever came first)
- Measurements following second treatment administration:
  - Hemodynamic parameters: HR, SAP, DAP, MAP, CVPm, PAPs, PAPd, PAPm, PAWPm, and CO
- Measurements following third treatment administration:
  - Hemodynamic parameters: HR, SAP, DAP, MAP, CVPm, PAPs, PAPd, PAPm, PAWPm, and CO
  - Arterial pH
- Measurements 1 and 3 years after the diagnostic procedure:
  - Therapies received since the diagnostic procedure
  - Date of surgery (if any)
  - Vital status and date of death, if applicable

9.5.2. Recording of Adverse Events

Each patient was assessed for any new or continuing AEs by the investigator or study coordinator. An AE was defined as any untoward medical occurrence. An AE need not have a causal relationship with treatment and included any event that was not seen at baseline or, if present at baseline, increased in severity. Any AE reported by the caregiver or noted by the investigator or study coordinator was recorded on the AE pages in the CRF. The severity and drug relationship were determined and any management required was also noted. Each AE was followed until resolution or discontinuation of study drug, whichever occurred first. The investigator also reviewed clinical laboratory test results and those qualifying as AEs were recorded in the AE section of the CRF.

9.5.2.1. Relationship of Adverse Events to Study Drug

The investigator was responsible for assessing the causal relationship between AEs and study treatment. Additionally, the investigator was responsible for providing appropriate treatment for the event and for adequately following the event until resolution. The investigator determined the study drug relationship to AEs using the following explanations:

- Not related: the event was clearly related to other factors, such as the patient's clinical state, therapeutic interventions, or concomitant drugs administered.
- Remote: the event was most likely produced by other factors, such as the patient's clinical state, therapeutic interventions, or concomitant drugs administered and did not follow a known response pattern to the study drug.
- Possible: the event followed a reasonable temporal sequence from the time of study drug administration or a known response pattern to the study drug, but could have been produced by other factors, such as the patient's clinical state, therapeutic interventions, or concomitant drugs administered.
- Probable: the event followed a reasonable temporal sequence from the time of study drug administration or a known response pattern to the study drug and could not be reasonably explained by other factors, such as the patient's clinical state, therapeutic interventions, or concomitant drugs administered.
- Highly probable: the event followed a reasonable temporal sequence from the time of study drug administration or a known response pattern to the study drug and could not be reasonably explained by other factors, such as the patient's clinical state, therapeutic interventions, or concomitant drugs administered; and either occurred immediately following study drug administration, improved following stopping the drug, or reappeared upon repeat exposure.

Temporal sequence was defined as an association between the suspect drug and the observed reaction in which the suspect drug was present prior to the reaction or event.

9.5.2.2. Severity of Adverse Events

Severity of an AE was defined from the qualitative assessment of the degree of intensity of the event as determined by the investigator or reported to him or her by the patient. The assessment of severity was made irrespective of drug relationship or seriousness of the AE and was evaluated according to the following categories:

- Mild: awareness of the symptom, but easily tolerated
- Moderate: discomfort enough to interfere with normal activities
- Severe: incapacitating with the inability to perform normal activities

9.5.2.3. Serious Adverse Events

An SAE was defined as any event that resulted in death, was life threatening, resulted in permanent disability or incapacity, required or prolonged inpatient hospitalization, or was a congenital anomaly. Important medical events that, without medical or surgical intervention, would also have resulted in one of the outcomes listed above were also considered as SAEs. All

SAEs occurring during the study and within 12 hours after discontinuation of treatment gas or hospital discharge, whichever came first, were to be reported to INO Therapeutics LLC within 24 hours by fax or telephone.

Patients were monitored carefully until SAEs resolved, reached a clinically stable endpoint, or the etiology was defined. The initial telephone contact was followed within 24 hours by completion of an SAE packet with detailed descriptions of the event and supported as needed with written copies of hospital case reports, autopsy reports, and other documents, as applicable.

All SAEs were reported to the IRB/IEC and appropriate local regulatory agency in writing.

9.5.2.4. Unexpected Adverse Events

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

All unexpected AEs were reported to the IRB/IEC and appropriate local regulatory agency in writing.

9.5.3. Appropriateness of Measurements

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

9.5.4. Efficacy Variables

9.5.4.1. Primary Efficacy Variable

The primary efficacy variable was the number of patients receiving a combination of NO and O_2 versus the number of patients receiving O_2 alone that met response criteria for a pulmonary vasoreactivity response. The response criteria were as follows:

- Patients with IPAH or patients with CHD who did not have an unrestricted shunt at the level of the ventricle or ductus arteriosus: a decrease in PAPm ≥20% and no decrease in CI (within 5%)
- Patients with cardiomyopathy or CHD who had an unrestricted shunt at the level of the ventricle or ductus arteriosus: a decrease in PAPm ≥20% and no decrease in CI (within 5%) or a decrease in PVRI ≥25% and no decrease in CI (within 5%)

9.5.4.2. Secondary Efficacy Variables

Secondary efficacy variables included:

- The number of patients receiving NO versus the number of patients receiving O_2 that met response criteria, as defined above
- The number of patients receiving a combination of NO and O_2 versus the number of patients receiving NO alone that met response criteria, as defined above

- PVRI, PAPm, and CI readings in room air versus NO alone, O_2 alone, and the combination of NO and O_2
- Change in the ratio of PAPm to MAP by treatment
- Survival at 1 and 3 years by response

9.5.5. Drug Concentration Measurements

The INOvent® gas delivery system measures the flow of gas in the ventilator circuit and a mass flow controller adds NO to the ventilator gas flow to create the desired concentration. The device continuously samples gas from the side port adapter and measures O_2, NO, and NO_2 with electrochemical monitors.

9.5.6. Safety Variables

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

- Incidence and types of reported SAEs
- Incidence and types of reported drug-related AEs

9.6. Data Quality Assurance

Prior to study initiation, meetings were carried out to prepare investigators and standardize performance at each study center. Data were collected by the study site coordinator and verified at the site by the clinical research associate (CRA). This data was monitored and verified 100% to the medical charts. Data were double key entered into a validated Oracle Clinical database managed by INO Therapeutics LLC. Discrepancies were flagged and the database manager made all decisions regarding flags. The trial staff at the hospital made data corrections as necessary.

INO Therapeutics LLC conducts clinical trials according to procedures that incorporate the ethical principles of GCP. To ensure compliance with these procedures and to assess the adequacy of quality control procedures, INO Therapeutics LLC undertakes a GCP audit program.

Audits are performed by a representative of INO Therapeutics LLC who operates independently of the trial monitors. The audits within a clinical program are aimed at trial documentation, investigator sites, and clinical trial reports.

The audit program, together with INO Therapeutics LLC's internal quality control procedures, provides reassurance that trial conclusions are based on valid procedures for data management and analysis, and that the clinical trial program is carried out in accordance with GCP guidelines.

9.7. Statistical Methods Planned in the Protocol and Determination of Sample Size

9.7.1. Statistical and Analytical Plans

All efficacy and safety analyses were carried out on all patients randomized (an intent-to-treat basis). The intent-to-treat population included all patients randomized regardless of actual receipt of treatment gas, the treatment gas actually received, or the appropriateness of their enrollment.

9.7.2. Analysis of Baseline Characteristics

The distributions of all baseline characteristics (age, sex, race, etc.) were tabulated for all patients in the intent-to-treat population.

9.7.3. Primary Efficacy Analysis

The primary efficacy variable for this trial was the number of patients that met criteria for a pulmonary vasoreactivity response (see Section 9.5.4.1). The difference in the primary efficacy variable between treatment with NO plus O_2 versus O_2 alone was compared with the McNemar Test for Significance of Changes. This test was conducted with a type I (α) error of 0.05 for statistical significance (2-tailed).

9.7.4. Secondary Efficacy Analyses

Analysis of all secondary efficacy variables was conducted with a type I (α) error of 0.05 for statistical significance (2-tailed).

The numbers of patients who met the response criteria for a pulmonary vasoreactivity response during treatment with NO versus O_2 and NO versus NO plus O_2 were compared with the McNemar Test for Significance of Changes. These tests were conducted with a type I (α) error of 0.05 for statistical significance (2-tailed).

Differences in PVR, PAPm, and CO in room air versus each treatment were compared with paired t-tests if the normality assumption was not violated, or the Wilcoxon Signed Ranks test if there was a violation of normality. All tests were conducted with a type I (α) error of 0.05 for statistical significance (2-tailed).

The difference in the ratios of PAPm to MAP for the NO plus O_2 versus O_2 was analyzed using an analysis of variance (ANOVA) model. The list of independent variables included treatment, patient (nested within treatment sequence), and treatment sequence. Differences among treatments were assessed with a type I (α) error of 0.05 for statistical significance (2-tailed).

9.7.5. Adverse Events

Analysis of AEs was performed on the number and types of all AEs, treatment-related AEs, and SAEs reported during each treatment. The incidences of all AEs, treatment-related AEs, and SAEs were stratified by MedDRA terms, MedDRA body system, and patients with each type of

AE were tabulated. Additionally, all AEs, treatment-related AEs, and SAEs were stratified by age, sex and race.

9.7.6. Determination of Sample Size

The following assumptions were made:

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

Using the assumptions listed above, the minimum number of patients required per entry diagnosis was 25. Enrollment proceeded until at least 25 patients per entry diagnosis were enrolled and there were at least 100 patients in the trial.

9.7.7. Interim Analyses

No interim analyses were carried out.

9.8. Changes in the Conduct of the Study or Planned Analyses

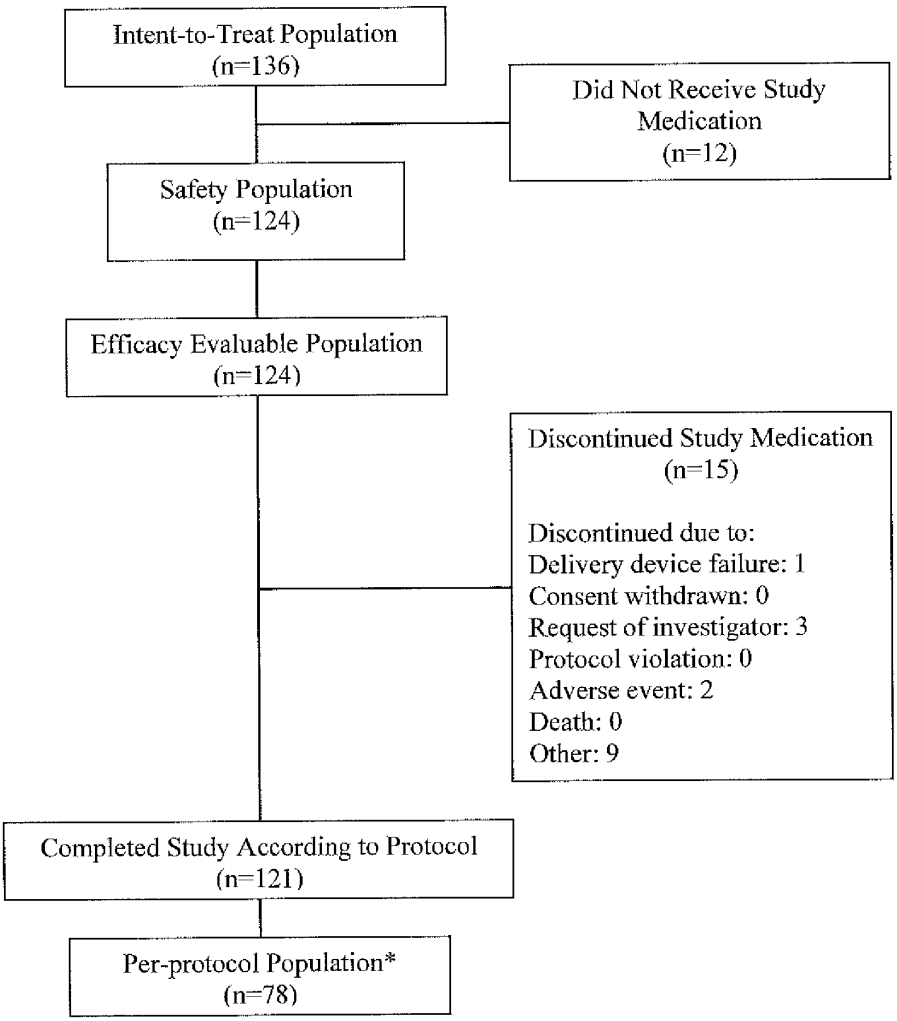
There were no significant changes in the planned conduct of the study or in any analyses.

10. STUDY PATIENTS

10.1. Disposition of Patients

Patient disposition is summarized in Figure 2 and Table 3. The intent-to-treat population included 136 patients and the safety and efficacy-evaluable populations each included 124 patients. Overall, 121 (89.0%) patients completed the study. The per-protocol population consisted of all study completers who had a baseline PVRI > 3. The most common reason for discontinuation was request of the investigator (2.2%) followed by AEs (1.5%).

Figure 2: Patient Disposition



* The per-protocol population had a baseline PVRI > 3. The other 43 patients who completed the study according to the protocol did not have the required PVRI at baseline.

Table 3: Patient Disposition and Reasons For Discontinuation

Analysis Population	Number (%)
ITT	136 (100)
Safety	124 (91.2)
Efficacy Evaluable[a]	124 (91.2)
Per-protocol[b]	78 (57.4)
Completed Study According to Protocol	121 (89.0)
Discontinued Study Medication	15 (11.0)
Primary Reason For Discontinuation	
Delivery Device Failure	1 (0.7)
Consent Withdrawn	0 (0.0)
Request of Investigator	3 (2.2)
Protocol Violation	0 (0.0)
AE	2 (1.5)
Death	0 (0.0)
Other	9 (6.6)

[a] Patients who took study medication
[b] Patients with baseline PVRI > 3
Source: Section 14.1, Table 1, and Appendix 16.2.1

10.2. Protocol Deviations

A total of 123 protocol deviations occurred, none of which required exclusion of patients from the efficacy evaluable population. Deviations from the protocol were categorized as follows:

- Informed Consent (n = 34; most frequently, the use of an outdated Informed Consent Form)
- Inclusion/Exclusion Criteria (n = 6; missed diagnoses of either the underlying cardiovascular condition or pulmonary disease; use of an excluded medication)
- Study Procedures and Examinations (n = 75; most frequently, incorrect timing of measurements; pregnancy test not performed; and PaO_2 not determined)
- Device Use and Maintenance (n = 5; missed monthly calibration of equipment and related)
- SAE Reporting and Documentation (n = 3)

A complete listing of protocol deviations can be found in Appendix 16.2.2.

11. EFFICACY EVALUATION

11.1. Data Sets Analyzed

11.1.1. Study Gas Exposure

The mean times for exposure to study gas were very similar for NO plus O_2 (15.5 minutes), O_2 (15.9 minutes), and NO (15.3 minutes) (Table 4).

Table 4: Study Gas Exposure By Treatment (Intent-to-Treat)

Treatment Duration (minutes)[a]	NO Plus O_2	O_2	NO
N	123	122	123
Mean	15.5	15.9	15.3
SD	5.53	6.54	4.90
Median	14.0	15.0	15.0
Minimum, maximum	5.0, 33.0	7.0, 51.0	8.0, 34.0

[a] Duration (minutes) = (stop time of treatment – start time of treatment) + 1
Source: Section 14.1, Table 2

11.2. Demographic and Other Baseline Characteristics

The demographic and baseline characteristics of the intent-to-treat and per-protocol populations are summarized in Tables 5 and 6. The mean age for the patients in the intent-to-treat population was 5.9 years, 50.0% were male, 59.6% were white, and 40.4% were black. The diagnosis was IPAH in 22.1%, cardiomyopathy in 4.4%, and CHD with PH in 73.5%.

Table 5: Demographics and Baseline Characteristics (Intent-to-Treat)

Characteristic	Intent-to-Treat Population (n=136)
Age (years)	
Mean	5.9
SD	5.58
Median	3.4
Minimum, maximum	0.1, 18.7
≤ 10 (n [%])	98 (72.1)
> 10 (n [%])	38 (27.9)

Table 5: Demographics and Baseline Characteristics (Intent-to-Treat) (Continued)

Characteristic	Intent-to-Treat Population (n=136)
Sex (n [%])	
Male	68 (50.0)
Female	68 (50.0)
Race (n [%])	
White	81 (59.6)
Black	55 (40.4)
Height (cm)	
Mean	101.6
SD	38.02
Median	93.8
Minimum, maximum	50.0, 181.0
Weight (kg)	
Mean	20.0
SD	17.23
Median	14.0
Minimum, maximum	2.7, 70.0
Diagnosis (n [%])	
IPAH	30 (22.1)
Cardiomyopathy	6 (4.4)
CHD With PH	100 (73.5)
Shunt	75 (75.0)
No Shunt	25 (25.0)
Baseline Hgb (g/dL)	
Mean	12.7
SD	2.31
Median	12.5
Minimum, maximum	7.8, 21.0

Table 5: Demographics and Baseline Characteristics (Intent-to-Treat) (Continued)

Characteristic	Intent-to-Treat Population (n=136)
Supplemental O_2 (n [%])	
Yes	30 (22.1)
No	106 (77.9)
Diagnosis Method (n [%])	
Fick	103 (75.7)
Thermodilution	29 (21.3)
Missing	4 (2.9)

Source: Section 14.1, Table 3.1 and Appendix 16.2.4.

The mean age for the patients in the per-protocol population was 7.4 years, 48.7% were males, 65.4% were white and 34.6% were black. The diagnosis was IPAH in 32.1%, cardiomyopathy in 1.3%, and CHD with PH in 66.7%.

Table 6: Demographics and Baseline Characteristics (Per-protocol)

Characteristic	Per-protocol (n=78)
Age (years)	
Mean	7.4
SD	5.80
Median	8.1
Minimum, maximum	0.1, 18.7
≤10 (n [%])	47 (60.3)
>10 (n [%])	31 (39.7)
Sex (n [%])	
Male	38 (48.7)
Female	40 (51.3)
Race (n [%])	
White	51 (65.4)
Black	27 (34.6)
Height (cm)	
Mean	110.9

Characteristic	Per-protocol (n=78)
SD	39.13
Median	115.8

Table 6: Demographics and Baseline Characteristics (Per-protocol) (Continued)

Characteristic	Per-protocol (n=78)
Minimum, maximum	50.0, 181.0
Weight (kg)	
Mean	23.9
SD	18.42
Median	21.5
Minimum, maximum	2.7, 70.0
Diagnosis (n [%])	
IPAH	25 (32.1)
Cardiomyopathy	1 (1.3)
CHD With PH	52 (66.7)
Shunt	34 (65.4)
No Shunt	18 (34.6)
Baseline Hgb (g/dL)	
Mean	13.3
SD	2.46
Median	13.3
Minimum, maximum	7.8, 21.0
Supplemental O_2 (n [%])	
Yes	19 (24.4)
No	59 (75.6)
Diagnosis Method (n [%])	
Fick	55 (70.5)
Thermodilution	23 (29.5)

Source: Section 14.1, Table 3.2 and Appendix 16.2.4

11.2.1. Concomitant Medications

Concomitant medications are summarized in Table 7. The most common concomitant medications were heparin, sevoflurane, fentanyl, propofol, midazolam, nalbuphine, atropine, chloral hydrate, midazolam hydrochloride, vecuronium, paracetamol, cefamandole, and furosemide.

Table 7: Concomitant Medications During The Study Period (Intent-to-Treat)

Medication[a, b] (n [%])	Intent-to-Treat Population (n=136)
Heparin	67 (49.3)
Sevoflurane	47 (34.6)
Fentanyl	44 (32.4)
Propofol	44 (32.4)
Midazolam	41 (30.1)
Nalbuphine	34 (25.0)
Atropine	23 (16.9)
Chloral Hydrate	22 (16.2)
Midazolam Hydrochloride	18 (13.2)
Vecuronium	16 (11.8)
Paracetamol	15 (11.0)
Cefamandole	14 (10.3)
Furosemide	13 (9.6)
Alfentanil Hydrochloride	10 (7.4)
Atracurium	9 (6.6)
Cisatracurium Besilate	9 (6.6)
Ondansetron Hydrochloride	9 (6.6)
Clorazepate Dipotassium	8 (5.9)
Morphine	8 (5.9)
Rocuronium	8 (5.9)
Diclofenac	7 (5.1)
Bosentan	6 (4.4)
Cefazolin	6 (4.4)
Hydroxyzine Hydrochloride	6 (4.4)
Lidocaine	6 (4.4)
Nifedipine	6 (4.4)

Medication[a, b] (n [%])	Intent-to-Treat Population (n=136)
Remifentanil	6 (4.4)
Sodium Bicarbonate	6 (4.4)

[a] A patient taking a medication multiple times is counted only once for that medication.
[b] Medications taken by > 5 patients
Source: Section 14.1, Table 4 and Appendix 16.2.5

11.3. Measurements of Treatment Compliance

Of the 136 patients enrolled into this study, 124 received study medication according to protocol. The time on treatment ranged between 5 to 33 minutes for patients on NO plus O_2, between 7 and 51 minutes for patients on O_2 alone, and between 8 and 34 minutes for patients on NO only.

11.4. Efficacy Results and Tabulations of Individual Patient Data

11.4.1. Analysis of Efficacy

11.4.2. Primary Efficacy Variable

The primary objective was to compare the number of patients with reversible pulmonary hypertension (vasoreactivity) demonstrated by NO for inhalation 80 ppm plus O_2 90% as compared to 100% O_2 alone. Study results for the intent-to-treat population (Table 8) indicated a significantly higher response rate (25.7%) for NO plus O_2 versus O_2 alone (14.7%) ($p = 0.019$). In addition, 17.4% of patients responded only to NO plus O_2 versus 6.4% who only responded to O_2 alone.

Table 8: Pulmonary Vasoreactivity Response By Treatment - NO Plus O_2 Versus O_2 (Intent-to-Treat)

Treatment: NO Plus O_2 (n=109)			
	Nonresponder (n [%])	**Responder[a] (n [%])**	**p-value[b]**
Treatment: O_2			
Nonresponder	74 (67.9)	19 (17.4)	0.019
Responder	7 (6.4)	9 (8.3)	

[a] At least a 20% reduction in PAPm as compared to baseline and no decrease in CI (within 5%) for all patients or at least a 25% reduction in PVRI and no decrease in CI (within 5%) for patients with cardiomyopathy or patients with CHD who have an unrestricted shunt at the level of the ventricle or ductus arteriosus.

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

Source: Section 14.2.1, Table 5.1.1 and Appendix 16.2.6

Baseline pulmonary vascular resistance is a clinically important indicator of disease severity. Because a significant proportion of patients in this study had a baseline PVRI lower than that required for enrollment into the study, the overall disease severity is likely to be somewhat lower than that which had been expected at study inception. For this reason, we decided to include analyses of the 'per-protocol' population. Similar trends were noted for response in the per-protocol population as in the ITT population. There was a higher response rate (22.2%) for NO plus O_2 versus O_2 alone (11.5%). The magnitude of this effect appears to be greater than that seen in the ITT population, but this difference did not achieve statistical significance ($p = 0.071$) due to the smaller sample size (Table 9). In this population, 15.3% of patients responded only to NO plus O_2 versus 4.6% who responded only to O_2.

Table 9: Pulmonary Vasoreactivity Response By Treatment - NO Plus O_2 Versus O_2 (Per-protocol)

Treatment: NO Plus O_2 (n=72)			
	Nonresponder (n [%])	**Responder[a] (n [%])**	**p-value[b]**
Treatment: O_2			
Nonresponder	52 (72.2)	11 (15.3)	0.071
Responder	4 (4.6)	5 (6.9)	

[a] At least a 20% reduction in PAPm as compared to baseline and no decrease in CI (within 5%) for all patients or at least a 25% reduction in PVRI and no decrease in CI (within 5%) for patients with cardiomyopathy or patients with CHD who have an unrestricted shunt at the level of the ventricle or ductus arteriosus.

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

Source: Section 14.2.1, Table 5.1.2 and Appendix 16.2.6

The presence or absence of a significant intracardiac shunt is another important clinical consideration. The majority of patients in this study had an intracardiac shunt. We analyzed the treatment effect in the subset of patients without a shunt. Results for NO plus O_2 versus O_2 alone for patients without shunts were similar to those for the overall population (Table 10). Overall, 22.5% of these patients responded to NO plus O_2 versus 8.2% for O_2 alone (p=0.035).

Table 10: Pulmonary Vasoreactivity Response By Treatment - NO Plus O_2 Versus O_2 - Patients Without Shunts, (Intent-to-Treat)

Treatment: NO Plus O_2 (n=49)			
	Nonresponder (n [%])	**Responder[a] (n [%])**	**p-value[b]**
Treatment: O_2			
Nonresponder	36 (73.5)	9 (18.4)	0.035
Responder	2 (4.1)	2 (4.1)	

[a] At least a 20% reduction in PAPm as compared to baseline and no decrease in CI (within 5%) for all patients or at least a 25% reduction in PVRI and no decrease in CI (within 5%) for patients with cardiomyopathy or patients with CHD who have an unrestricted shunt at the level of the ventricle or ductus arteriosus.

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

Source: Section 14.2.1 Table 5.1.3 and Appendix 16.2.6

Results for NO plus O_2 versus O_2 alone for patients without shunts in the per-protocol population were similar to those for the overall population (Table 11). Overall, 21.9% of these patients responded to NO plus O_2 versus 4.8% for O_2 alone (p=0.020).

Table 11: Pulmonary Vasoreactivity Response By Treatment - NO Plus O_2 Versus O_2 - Patients Without Shunts (Per-protocol)

Treatment: NO Plus O_2 (n=41)			
	Nonresponder (n [%])	**Responder[a] (n [%])**	**p-value[b]**
Treatment: O_2			
Nonresponder	31 (75.6)	8 (19.5)	0.020
Responder	1 (2.4)	1 (2.4)	

[a] At least a 20% reduction in PAPm as compared to baseline and no decrease in CI (within 5%) for all patients or at least a 25% reduction in PVRI and no decrease in CI (within 5%) for patients with cardiomyopathy or patients with CHD who have an unrestricted shunt at the level of the ventricle or ductus arteriosus.

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

Source: Section 14.2.1, Table 5.1.4 and Appendix 16.2.6

11.4.3. Secondary Efficacy Variables

There was no significant difference between responsivity to NO alone versus O_2 alone in the intent-to-treat population (Table 12). The response rate for NO was 23.6% and that for O_2 was 15.1% (p=0.117). For this comparison, 19.8% of patients responded only to NO versus 11.3% for O_2.

Table 12: Pulmonary Vasoreactivity Response By Treatment - NO versus O_2 (Intent-to-Treat)

Treatment: NO (n=106)			
	Nonresponder (n [%])	**Responder[a] (n [%])**	**p-value[b]**
Treatment: O_2			
Nonresponder	69 (65.1)	21 (19.8)	0.117
Responder	12 (11.3)	4 (3.8)	

[a] At least a 20% reduction in PAPm as compared to baseline and no decrease in CI (within 5%) for all patients or at least a 25% reduction in PVRI and no decrease in CI (within 5%) for patients with cardiomyopathy or patients with CHD who have an unrestricted shunt at the level of the ventricle or ductus arteriosus.

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

Source: Section 14.2.2, Table 5.2.1 and Appendix 16.2.6

Overall results for the per-protocol population supported those for the intent-to-treat population. The response rates for NO and O_2 were 15.5% and 12.7%, respectively (p = 0.617). In this population, 12.7% of patients responded only to NO versus 9.9% for O_2.

Results for patients without shunts in the intent-to-treat population indicated that 27.1% responded to NO and 8.4% responded to O_2 (p = 0.020).

Comparison of results for NO alone versus NO plus O_2 in the intent-to-treat population indicated no significant differences in pulmonary vasoreactivity response (Table 13). The response rate for NO was 24.1% and that for NO plus O_2 was 26.9% (p = 0.602). In this comparison, 13.9% of patients responded only to NO versus 16.7% for NO plus O_2.

Table 13: Pulmonary Vasoreactivity Response By Treatment - NO Versus NO Plus O_2 (Intent-to-Treat)

Treatment: NO Plus O_2 (n=108)			
	Nonresponder (n [%])	**Responder[a] (n [%])**	**p-value[b]**
Treatment: NO			
Nonresponder	64 (59.3)	18 (16.7)	0.602
Responder	15 (13.9)	11 (10.2)	

[a] At least a 20% reduction in PAPm as compared to baseline and no decrease in CI (within 5%) for all patients or at least a 25% reduction in PVRI and no decrease in CI (within 5%) for patients with cardiomyopathy or patients with CHD who have an unrestricted shunt at the level of the ventricle or ductus arteriosus.

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

Source: Section 14.2.2, Table 5.3.1 and Appendix 16.2.6

Results for the per-protocol population supported those for the ITT population. The response rate for NO was 16.4% and that for NO plus O_2 was 23.3% ($p = 0.251$). In this population, 9.6% of patients responded only to NO versus 16.4% for NO plus O_2

Results for patients without shunts in the intent-to-treat population indicated that 24.0% responded to NO plus O_2 and 28.0% responded to NO alone ($p = 0.617$).

There was no significant difference in the rate of pulmonary vasoreactivity for patients with or without shunts in either the intent-to-treat or per-protocol populations. In the intent-to-treat population, 45.9% of patients with shunts responded to at least one intervention, versus 46.2% of those without shunts ($p = 1.000$). The respective values for the per-protocol population were 38.7% and 39.5% ($p = 1.000$).

There was no significant difference in the rate of pulmonary vasoreactivity for patients with or without intubation in either the intent-to-treat or per-protocol populations. In the intent-to-treat population, 39.7% of intubated patients responded to at least one intervention versus 52.7% of those who were not intubated ($p = 0.189$). The respective values for the per-protocol population were 33.3% and 43.9% ($p = 0.473$).

Diagnosis significantly influenced the rate of pulmonary vasoreactivity in the intent-to-treat population (Table 14). In the intent-to-treat population, response rates were 42.0%, 48.1%, and 100% for patients with CHD, idiopathic disease, and cardiomyopathy, respectively ($p = 0.034$). The respective values in the per-protocol population were 35.4%, 44.0%, and 100% ($p = 0.366$).

Table 14: Pulmonary Vasoreactivity By Diagnosis (Intent-to-Treat)

	Diagnosis			
	CHD (n [%])	**Idiopathic (n [%])**	**Cardiomyopathy (n [%])**	**p-value[b]**
Response				
Responder[a]	34 (42.0)	13 (48.1)	5 (100.0)	0.034
Nonresponder	47 (58.0)	14 (51.9)	0 (0)	

[a] At least a 20% reduction in PAPm as compared to baseline and no decrease in CI (within 5%) for all patients or at least a 25% reduction in PVRI and no decrease in CI (within 5%) for patients with cardiomyopathy or patients with CHD who have an unrestricted shunt at the level of the ventricle or ductus arteriosus.

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

Source: Section 14.2.2, Table 5.6.1 and Appendix 16.2.6

All treatments significantly decreased PVRI (Figure 3 and Tables 15 and 16). In the intent-to-treat population, the mean changes from baseline with NO plus O_2, O_2 and NO were -2.9, -1.5, and -1.1 $WU \cdot m^2$, respectively (all $p<0.001$ versus baseline). The between-treatment comparisons were also significantly different. The NO plus O_2 was significantly different than both NO and O_2 alone ($p = <0.001$). However, NO alone was not significantly different from O_2 alone ($p = 0.171$). Patients with no shunt provided similar results. A scatter plot of the PVRI change from baseline comparing NO plus O_2 versus O_2 alone is presented in Figure 4.

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

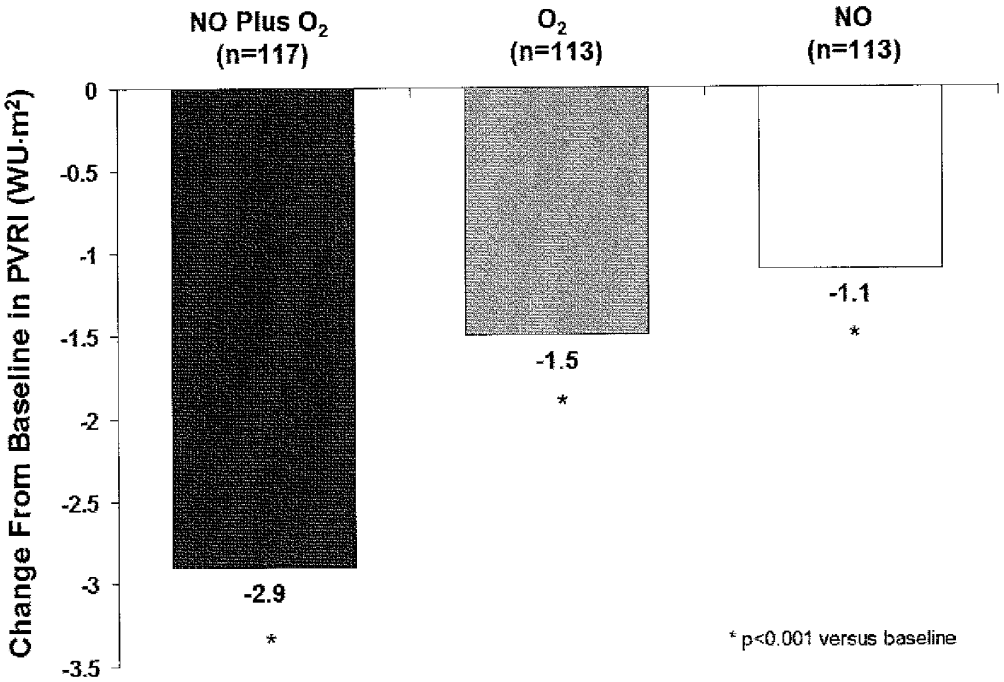


Table 15: PVRI Change From Baseline By Treatment (Intent-to-Treat)

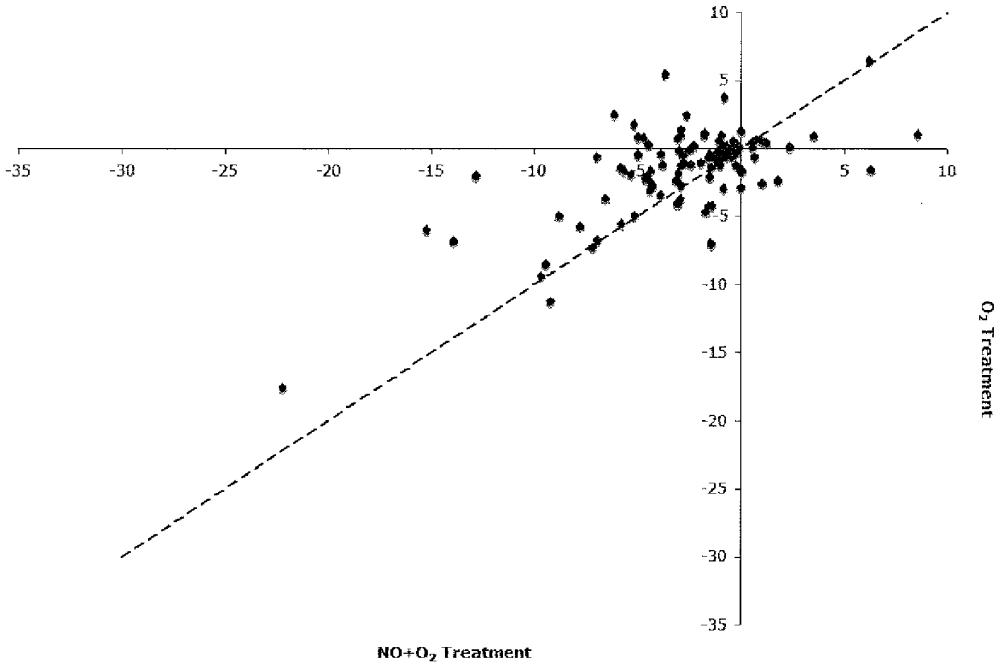
	Treatment		
PVRI ($WU \cdot m^2$)	**NO Plus O_2 (n=117)**	**O_2 (n=113)**	**NO (n=113)**
Baseline (room air)			
Mean	10.8	10.0	10.3
SD	10.30	9.65	10.33
Median	7.5	6.9	6.6
Minimum, maximum	0.5, 54.0	0.5, 47.7	0.9, 54.0
Post-treatment			
Mean	7.8	8.5	9.2
SD	8.75	8.63	10.45
Median	3.6	5.5	5.6
Minimum, maximum	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)



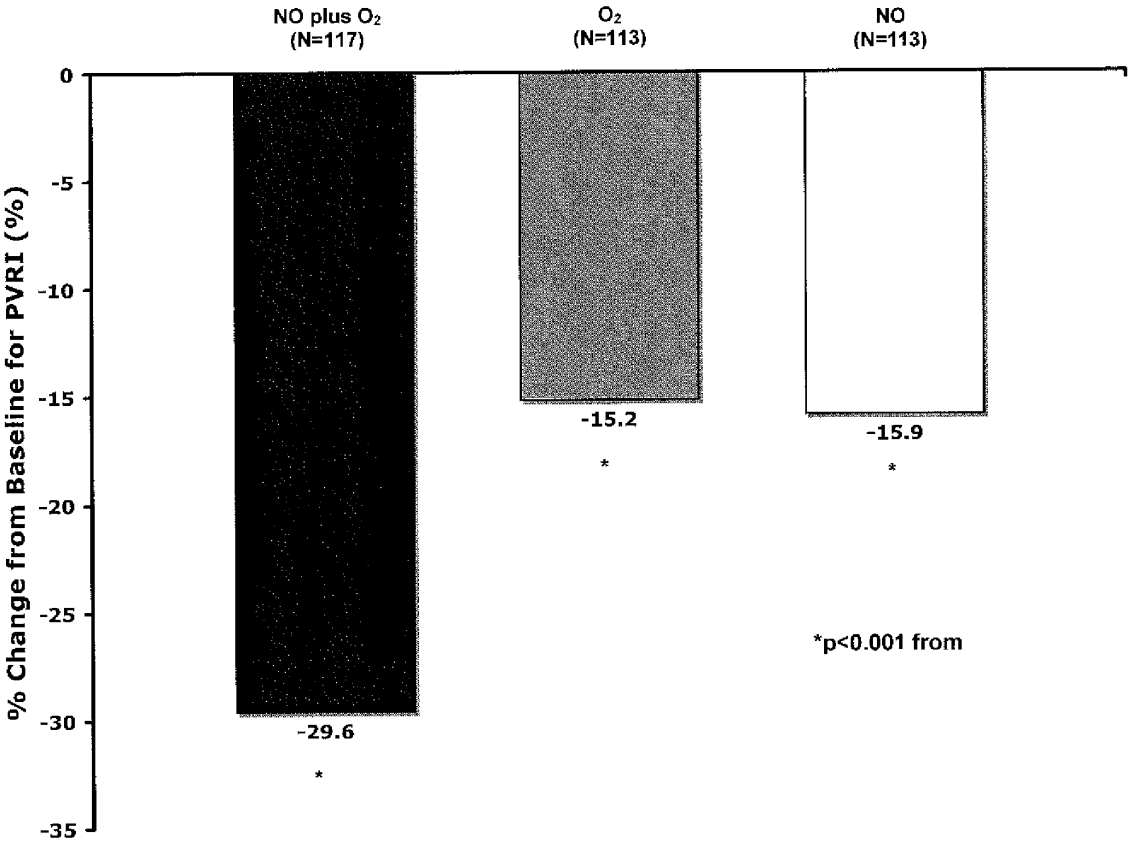
The mean percent changes from baseline in PVRI for the intent-to-treat population (Table 16 and Figure 5) were -29.6%, -15.2%, and -15.9% for NO plus O2, O2, and NO, respectively (all p<0.001 versus baseline).

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 $WU \cdot m^2$ ($p = 0.007$) and that for O_2 was 1.3 $WU \cdot m^2$ ($p = 0.004$). The change from baseline in SVRI with NO was -0.2 $WU \cdot m^2$ ($p = 0.889$).

Table 19: 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
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 $WU \cdot m^2$, 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 $WU \cdot m^2$ (p=0.007) and that for O_2 was 1.3 $WU \cdot m^2$ (p=0.004). The change from baseline in SVRI with NO was -0.2 $WU \cdot m^2$ (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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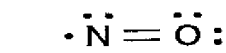
INOmax® (nitric oxide) for inhalation
100 and 800 ppm (parts per million)

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.

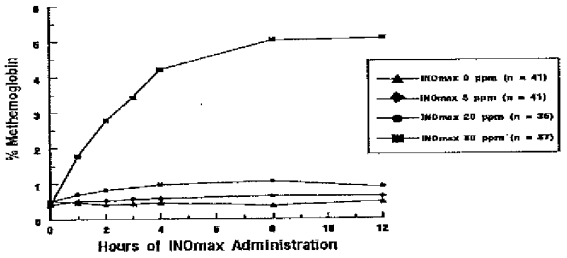
Effects on Pulmonary Vascular Tone in PPHN
Persistent pulmonary hypertension of the newborn (PPHN) occurs as a primary developmental defect or as a condition secondary to other diseases such as meconium aspiration syndrome (MAS), pneumonia, sepsis, hyaline membrane disease, congenital diaphragmatic hernia (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%)	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

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

EXHIBIT B

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	: James S. Baldassarre	Art Unit	: 1613
Serial No.	: 13/683,236	Examiner	: Ernst V. Arnold
Filed	: November 21, 2012	Conf. No.	: 5655
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 OF DOUGLAS A. GREENE, M.D. UNDER 37 C.F.R. § 1.132

I, Douglas A. Greene, do hereby declare the following:

1. I currently hold the position of Executive Vice President and Head of Research and Development at INO Therapeutics LLC ("INO"), which is a wholly-owned subsidiary of Ikaria, Inc. A copy of my *curriculum vitae* is attached as **Appendix 1**.

2. I received an undergraduate degree in biology (*cum laude*) from Princeton University in 1966 and a doctoral degree in medicine (M.D.) from Johns Hopkins School of Medicine in 1970.

3. I spent the next thirty years of my medical career (1970-2000) practicing and teaching medicine at some of America's foremost academic medical centers, including Johns Hopkins, the University of Pennsylvania, the University of Pittsburgh, and the University of Michigan. At Michigan, I was a full professor of internal medicine, director of the Michigan Diabetes Research and Training Center, and chief of the Division of Endocrinology and Metabolism.

4. In 2000, I left Michigan to join Merck as Executive Vice President in charge of clinical sciences and product development. In this role, I supervised and directly managed all clinical research at Merck Research Laboratories, among other duties.

5. In 2003, I left Merck for Sanofi-Aventis, where I became a Senior Vice President and Chief Medical Officer. My duties at Sanofi-Aventis included overseeing all aspects of pre-clinical and clinical regulatory development of the company's products and overseeing all medical aspects of the company's US business.

6. In 2010, I joined INOT, where – as noted above – I am presently Executive Vice President and Head of Research and Development.

7. I have been shown a Final Office Action issued by the United States Patent and Trademark Office (USPTO) on April 24, 2013 (the "Office Action") in the present patent application. This Office Action rejected the then-pending claims as "obvious" based on clinical interpretations presented by the USPTO regarding the disclosure of several documents: a 2008 Belgian marketing authorization for a nitric oxide gas product with the trade name "VasoKINOX" (hereafter, "VasoKINOX"); Kazerooni et al. (Cardiopulmonary Imaging 2004, Lippincott Williams & Wilkins, pages 234 and 236 in part; "Kazerooni et al."); Loh et al. (Circulation 1994, 90, 2780-2785; "Loh et al."); Leo (Primary Care Companion, J Clin Psychiatry 1999, 1:5; pages 131-141; "Leo"); Himashree et al. (Current Science 2003, 85, 5, pages 607-614; "Himashree et al."); and McLaughlin et al. (Circulation 2006, 114, pages 1417-1431; "McLaughlin et al."). Below is my professional opinion of the arguments and clinical interpretations presented by the USPTO in the Office Action.

8. On page 7 of the Office Action, the USPTO states:

> *VasoKINOX teaches methods of ... treating pulmonary hypertension, a form of hypoxic respiratory failure.*

This is a misreading of what VasoKINOX teaches. Pulmonary hypertension is not "a form of hypoxic respiratory failure," and VasoKINOX does not say--nor even imply--that it is. VasoKINOX says nothing about hypoxic respiratory failure or anything that is a "form of" the latter condition. The medical indication that is the entire focus of VasoKINOX is **perioperative and postoperative pulmonary hypertension in the context of cardiac surgery**. This is entirely distinct from **hypoxic respiratory failure**.

9. **Pulmonary hypertension** refers to a condition in which the hydrostatic pressure of the blood within the pulmonary blood vessels is increased. This condition can have many very different proximal causes and can be associated with many very different categories of conditions. See, e.g., the various World Health Organization categories of pulmonary hypertension and associated conditions listed in Table 1 on page 1419 of McLaughlin et al. In contrast, **hypoxic respiratory failure** refers to any condition in which disease of the airways or the blood vessels of the lung impairs gas exchange leading to under-oxygenation of the blood (hypoxia). Pulmonary hypertension in the context of some of the conditions listed in Table 1 of McLaughlin et al. (e.g., **persistent pulmonary hypertension of the newborn**, or **PPHN**) can lead to hypoxic respiratory failure, but pulmonary hypertension in the context of many of the other listed conditions would not. Thus, while the two different conditions (**pulmonary hypertension** and **hypoxic respiratory failure**) can sometimes coexist in the same patient (as in PPHN), one certainly cannot say that either condition is a "form of" the other.

10. The indication that is the focus of VasoKINOX--**perioperative and postoperative pulmonary hypertension in the context of cardiac surgery**—is pulmonary hypertension that occurs during and after cardiac surgery in some patients by a mechanism that involves vasoconstriction, possibly due to decreased endogenous nitric oxide in the arterial vessels of the lungs. Pulmonary hypertension in this situation puts the patient at risk not of hypoxia or hypoxic respiratory failure, but rather of an overworked and overloaded right ventricle that has to pump at unduly high pressure against the constricted pulmonary arteries. Inhaling nitric oxide gas during and after the surgery supplies exogenous nitric oxide to the constricted pulmonary vessels, opening them up so that the patient's right ventricle can work efficiently and without undue stress to pump blood through the lungs after removal of the cardiopulmonary bypass.

11. In contrast to perioperative and postoperative pulmonary hypertension in the context of cardiac surgery, **hypoxic respiratory failure in neonates** typically occurs due to an abnormal persistence of the fetal cardiopulmonary physiology after birth. Prior to birth, the fetus' blood is

shunted from the right side of the heart directly to the left side and/or to the systemic circulation, rather than into the lungs, which are normally vasoconstricted until birth. At birth, the fetal shunts in the heart are supposed to close, permitting the right side of the heart to pump blood into the lungs instead of through the shunts, and the pulmonary vessels are supposed to relax so that the blood can flow relatively unimpeded through the lungs. When the fetal cardiopulmonary physiology persists after birth, normal blood flow through the lungs does not happen as it is supposed to. This means the blood does not get sufficiently oxygenated, resulting in **hypoxic respiratory failure** and a "blue baby." Inhaling nitric oxide can alleviate the hypoxic respiratory failure in such neonates by opening up the pulmonary blood vessels and thereby increasing blood flow from the right heart into the lungs. This decreases blood flow through the shunts and improves oxygenation.

12. In adults, left ventricular dysfunction is generally ischemic or hypertensive in origin, and is associated with a stiff, non-compliant left ventricle that cannot fill properly ("diastolic dysfunction"). Diastolic dysfunction is extremely common in adult heart disease, especially in the elderly, but is extremely rare in childhood heart disease, which is generally caused by either congenital malformations or viral infections.[i] In children, left ventricular dysfunction is generally not ischemic or hypertensive in origin and is not associated with impaired filling, but rather is associated with a soft, overly elastic heart that cannot push blood out, resulting in impaired emptying ("systolic dysfunction"). Thus, it was known in the art that adult left ventricular diastolic dysfunction, but not childhood left ventricular systolic dysfunction, would lead to pulmonary vascular engorgement, requiring caution in the use of inhaled NO. In contrast, it was believed that the soft, overly elastic left ventricle typical of childhood left ventricular dysfunction would be able to handle a sudden increase in blood volume resulting from inhaled

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[i] Diastolic dysfunction in children has been described in rare genetic diseases such as Marfan's syndrome [that directly affects the elasticity of connective tissue of the heart and elsewhere], Kawasaki's disease [that creates cardiac ischemia similar to that in adult ischemic cardiomyopathy] or sickle cell disease [that produces fibrotic scars in the myocardium].

NO treatment by simply expanding, with no particular risk of an increase in pulmonary artery wedge pressure.

13. The underlying etiologies and hemodynamic characteristics of both the primary heart disease and the increased pulmonary vascular resistance are drastically different in adults, as compared to non-adults, such that one cannot readily assume clinical results observed in adults will translate to neonates or children. In particular, left ventricular dysfunction in neonates with congenital heart disease is primarily due to developmental structural disease of the heart, inborn errors of metabolism that impair energy generation in the heart muscle, or viral infection. In contrast, Class III or class IV congestive heart failure in adults, e.g., the subjects in Loh et al., is due to ischemic or dilated cardiomyopathy, mostly secondary to coronary artery disease and/or chronic systemic hypertension. Pulmonary hypertension associated with neonatal congenital heart disease is secondary to chronic hypoxemia, developmental abnormalities of the pulmonary blood vessels and/or pulmonary vascular damage from abnormally high blood flow and/or pressure through the pulmonary vasculature, resulting in evident disease of the lung vasculature. In contrast, increased pulmonary vascular resistance in adult Class III or IV congestive heart failure is due to reactive pulmonary vasoconstriction secondary to increased sympathetic tone or circulating vasoactive molecules (Loh et al., p. 2780, left column) in otherwise structurally normal blood vessels. Therefore, the hemodynamic responses to pulmonary vasodilation by inhaled NO in children or neonates without right-to-left shunting of blood but with significant pulmonary hypertension and left ventricular dysfunction cannot be reasonably predicted from the hemodynamic responses to pulmonary vasodilation by inhaled NO of adults with advanced atherosclerotic congestive heart failure and reactive neuro-humoral pulmonary vascular constriction (with or without pulmonary hypertension) as described by Loh et al.

14. A treatment can be "contraindicated" in a given condition based on expected *lack of efficacy*, and need not involve an expected risk of harm. For example, the VasoKINOX contraindication for "all forms of pulmonary arterial hypertension due to pulmonary hyper-flow"

is likely based upon a realization in the art that inhaled nitric oxide would be ineffective at reducing pulmonary arterial hypertension that is attributable to pulmonary hyper-flow (high pressure from the right side of the heart or from a systemic-to-pulmonary shunt causing abnormally high blood flow through the lungs, which in turn causes pulmonary arterial hypertension). See, e.g., McLaughlin et al., page 1420, last paragraph. McLaughlin et al. also discusses pulmonary hypertension that is caused by back pressure in the context of left heart disease (page 1421, left column). McLaughlin et al. does not suggest using inhaled nitric oxide to reduce pulmonary hypertension in this situation, probably because the pulmonary hypertension does not involve vasoconstriction and so inhaled nitric oxide would be ineffective.

15. 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 were 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 any patent issuing on the present application.

Dated: December 2, 2013

Douglas A. Greene, M.D.

23074905.doc

APPENDIX 1

CURRICULUM VITAE

PERSONAL DATA

Name:	Douglas Alan Greene, M.D.

EDUCATION

High School	Columbia High School, South Orange, NJ, 1962
Undergraduate	Princeton University, Princeton, NJ, BA Biology(cum laude), 1962-1966
Graduate/Professional	Johns Hopkins School of Medicine, Baltimore, MD, M.D., 1966-1970

POSTDOCTORAL TRAINING

Medical Internship:	Department of Medicine, Johns Hopkins, Baltimore, MD, 1970-1971
Medical Residency:	Department of Medicine, Johns Hopkins, Baltimore, MD, 1971-1972
Fellowship:	Medical Fellowship, Department of Medicine, Johns Hopkins University, School of Medicine, Baltimore, MD, 1970-1972
	Post-doctoral Research Fellow, Diabetes, George S. Cox Medical Research Institute; Hospital of the University of Pennsylvania, Philadelphia, PA (Dr. Albert L Winegrad, preceptor), 1972-1975
	Medical Fellowship, Department of Medicine, University of Pennsylvania, School of Medicine, Philadelphia, PA, 1972-1975

NON-ACADEMIC EMPLOYMENT

2000-2003	Executive Vice President, Clinical Sciences and Product Development (CSPD), Merck Research Laboratories, Rahway, New Jersey, and Corporate Officer, Merck, Inc. Supervised and directly managed all clinical research, regulatory affairs, clinical and non-clinical quality assurance and pharmaco-vigilance at Merck Research Laboratories.

2003-2006 Vice President, Head Corporate Regulatory Development, Sanofi-Aventis, Bridgewater, NJ. Overseeing all aspects of corporate regulatory development of all pre-clinical and clinical development projects/life-cycle products in Research & Development.

2006-2009 Senior Vice President, Chief Medical Officer, Sanofi-Aventis, Bridgewater, NJ. Overseeing medical, regulatory, pharmacovigilance, risk management, education and medical communications for US region, Member US Executive Committee, Member Committee Operational de Development, International Clinical Development.

2009-present Senior Vice President, Senior Scientific Advisor, Sanofi-Aventis, Bridgewater, New Jersey. Member Corporate Portfolio Valuation Process and Drug Development Committees. The position at the interface between the Research and Development and Pharmaceutical Operations is responsible for providing key scientific and medical guidance for sanofi-aventis' scientific strategy within U.S. and global contexts to enhance the quality and effectiveness of the company's research and product portfolio, including assessment and guidance of internal R&D product pipeline and franchise portfolio and external commercial and academic innovation opportunities.

ACADEMIC APPOINTMENTS

1975-1980	Assistant Professor of Medicine, University of Pennsylvania, School of Medicine, Philadelphia, Pennsylvania
1980-1985	Associate Professor of Medicine, Director, General Clinical Research Center and Diabetes Research Laboratories, University of Pittsburgh, School of Medicine
1986-2000	Professor of Internal Medicine, Director, Michigan Diabetes Research and Training Center, University of Michigan School of Medicine
1991-2000	Chief, Division of Endocrinology & Metabolism, University of Michigan School of Medicine
2000-Present	Adjunct Professor, Internal Medicine, Division of Endocrinology & Metabolism, University of Michigan, School of Medicine

SELECTED SCIENTIFIC ACTIVITIES

1988-1994	Chairman, Endocrinologic and Metabolic Drug Advisory Board, Food and Drug Administration, Washington D.C (Chair, 1990-1994)
1994-2000	Chairman, Merck Scientific Board of Advisors

SELECTED SCIENTIFIC PRIZES AND AWARDS

1986	First Annual Raymond A. and Robert L. Kroc Lecturer, Eisenhower Medical Center, Palm Springs, California
1987	Moore Award, The American Association of Neuropathologists, Seattle, Washington
1987	Carol Sinicki Manuscript Award (The Diabetes Educator), American Association of Diabetes Educators, Chicago, Illinois
1988	Kellion Lecture, International Diabetes Federation, Sydney, Australia
1989	Banting and Best Lecture, Toronto General Hospital, Toronto, Canada
1994	Charles H. Best Lecturer, Toronto Diabetes Association, Toronto, Canada
1996	Invited Speaker, Seventy-fifth Anniversary Celebrating the Discovery of Insulin, Toronto, Canada
1996	First Alan Robinson Lecturer, University of Pittsburgh
1998	Outstanding Foreign Investigator Award, Japan Society of Diabetic Complications

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51. The Writing Team for the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group: Effect of intensive therapy on the microvascular complications of type 1 diabetes mellitus. *JAMA* 287:2563-2569, 2002.

EXHIBIT C

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	: James S. Baldassarre	Art Unit	: 1613
Serial No.	: 13/683,236	Examiner	: Ernst V. Arnold
Filed	: November 21, 2012	Conf. No.	: 5655
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 OF JAMES S. BALDASSARRE, M.D., UNDER 37 C.F.R. § 1.132

I, James S. Baldassarre, do hereby declare the following:

1. I am the inventor of the subject matter claimed in the present application.

2. I have over 25 years of experience as a physician, and over 15 years of experience directing clinical research in the pharmaceutical industry.

3. I held the position of Vice President of Clinical Research at Ikaria, Inc. (Ikaria), the assignee of U.S. Patent Application No. 12/821,020, from October 2003 until September 2013. I currently serve as a paid consultant of Ikaria and its subsidiary INO Therapeutics LLC, and retain an equity interest in the company. My *curriculum vitae* is attached as Exhibit 1.

4. Ikaria markets pharmaceutical grade nitric oxide (NO) gas under the brand name INOMAX® (nitric oxide) for inhalation. INOMAX® was approved by the U.S. Food and Drug Administration (FDA) in December 1999, after extensive clinical study and FDA review, 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 (ECMO).

5. Upon approval of INOMAX®, and up to the time the present invention was made, the INOMAX® label contained language communicating, in pertinent part, the following general warnings and contraindication:

INOmax® 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....

Methemoglobinemia increases with the dose of nitric oxide. ... Following discontinuation or reduction of nitric oxide the methemoglobin levels returned to baseline over a period of hours....

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

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

Thus, the original INOMAX® label did not include any warning or precaution with respect to a risk of pulmonary edema in patients with pre-existing left ventricular dysfunction (LVD).

6. In May 2004, INO Therapeutics LLC[1] (INOT) initiated a 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 the "INOT22" trial, to compare the utility and side effects of oxygen (O_2), inhaled NO, and a combination of inhaled NO and O_2 for determining pulmonary reactivity. I was the Medical Monitor responsible for the design and execution of the INOT22 study.

7. The INOT22 study was a randomized, multi-center study having an expected enrollment of 150 patients in approximately 18 study sites over approximately 2 years. The expected patient population for enrollment into the INOT22 study was subjects between the ages of four weeks and 18 years with idiopathic pulmonary arterial hypertension, congenital heart disease (with or without intravascular shunt) with pulmonary hypertension, or a cardiomyopathy, and who were undergoing diagnostic right heart catheterization scheduled to include acute pulmonary vasodilation testing to assess pulmonary vasoreactivity. The purpose of the study was to assess the safety and effectiveness of inhaled NO as a diagnostic agent in pediatric patients undergoing assessment of pulmonary hypertension (primary objective), and to confirm the hypothesis that inhaled NO is selective for the pulmonary vasculature (secondary objective).

[1] INO Therapeutics LLC is a wholly owned subsidiary of Ikaria, Inc., and holder of the NDA for INOMAX®.

8. The INOT22 study was established and designed by the study sponsor (INOT) and a Steering Committee comprising internationally recognized experts in the field of pediatric heart and lung disease, whose members assisted INOT in developing the INOT22 protocol, monitor the progress of the trial, and provide recommendations to INOT on changes in the procedures and conduct of the trial.

9. The Steering Committee consisted of:

a. David L. Wessel, MD, presently Senior Vice President, The Center for Hospital Based Specialties, and Division Chief, Pediatric Critical Care Medicine, at Children's National Medical Center, Washington, DC;

b. Robyn J. Barst, MD, formerly Professor Emeritus of Pediatrics and Medicine, Columbia University College of Physicians and Surgeons, New York; and

c. Duncan J. Macrae, MD, presently Director, Pediatric Intensive Care, Royal Brompton Hospital, London, UK.

10. The original INOT22 study protocol designed by INOT and the Steering Committee did not exclude study patients with pre-existing left ventricular dysfunction who were not dependent on right-to-left shunting of blood. The original INOT22 protocol designed by INOT and the Steering Committee contained the following inclusion and exclusion criteria:

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>3u·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).

Exclusion Criteria

The patent 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 +).

11. After the INOT22 study protocol design, but prior to study initiation and enrollment, the original INOT22 study protocol was reviewed by an Institutional Review Board (IRB) and/or Independent Ethics Committee (IEC) at each of the 18 participating study institutions, including review by the principal investigator within each study institution. In addition, prior to study initiation and enrollment, the original INOT22 study protocol was reviewed by the US Food and Drug Administration (FDA) and separately reviewed by each national Health Authority (European equivalent to FDA) within the four European countries participating in the INOT22 trial (United Kingdom, France, Netherlands and Spain). Further, INOT regularly requested input and scientific guidance on the clinical trial from its own

Scientific Advisory Board. At no time did any member of the Steering Committee, INOT, an IRB or IEC, an individual principal investigator, a Scientific Advisory Board member, FDA or European Health Authority suggest that subjects with pre-existing left ventricular dysfunction who are not dependent on right-to-left shunt should be excluded from the INOT22 study or that such subjects would be predicted to have an increased risk of adverse events or serious adverse events arising from the administration to them of inhaled nitric oxide.

12. Under FDA regulations, an IRB is an appropriately constituted group that has been formally designated to review and monitor biomedical research involving human subjects. In accordance with FDA regulations, an IRB has the authority to approve, require modifications in (to secure approval), or disapprove research. This group review serves an important role in the protection of the rights and welfare of human research subjects. The purpose of IRB review is to assure, both in advance and by periodic review, that appropriate steps are taken to protect the rights and welfare of humans participating as subjects in the research. To accomplish this purpose, IRBs use a group process to review research protocols to ensure protection of the rights and welfare of human subjects of research. An IRB must have at least five members and each member must have enough experience, expertise and diversity to make an informed decision on whether the research is ethical, informed consent is sufficient and the appropriate safeguards have been put in place (see 21 CFR Part 56).

13. In Europe, an IEC is an independent body in an EC Member State consisting of healthcare professionals and non-medical members whose responsibility is to protect the rights, safety and well-being of human subjects involved in a clinical trial and to provide public assurance of that protection by expressing an opinion on a proposed clinical trial protocol, the suitability of the investigators, and the adequacy of facilities involved in a trial (see Directive 2001/20/EC).

14. In total, at least 115 individuals experienced in and responsible for the review of clinical trial protocols for patient safety, in addition to the FDA and four European Health Authorities, reviewed the original INOT22 protocol prior to initiation of the INOT22 study.

Again, not a single individual or authority raised a concern about an increased risk associated with the use of inhaled nitric oxide in study subjects with pre-existing left ventricular dysfunction who were not dependent on right-to-left shunt.

15. After initiation and enrollment of the first 24 subjects in INOT22, there were 5 serious adverse events (SAEs) – a rate much higher than expected by INOT and the Steering Committee based on prior clinical experience. These were all cardiovascular events, and included pulmonary edema, cardiac arrest and hypotension (low blood pressure).

16. Thereafter, INOT and the Steering Committee convened to review the unexpected SAEs described above, and upon review and discussion, expressed concern that the unexpected SAEs may be due to the administration of inhaled NO in subjects having pre-existing LVD. Accordingly, based upon a review of the cases, the exclusion criteria of the INOT22 protocol were amended to thereafter exclude subjects with pre-existing LVD. For purposes of the study, the exclusion criteria were amended to exclude subjects from enrollment if the subjects demonstrated an elevated pulmonary capillary wedge pressure (PCWP), defined within the study as subjects having a PCWP greater than 20 mmHg. All study sites were notified immediately. The amended exclusion criteria, including the newly added criterion 5, were as follows:

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.***

17. Upon conclusion of the INOT22 study, INOT noted that, subsequent to excluding patients with pre-existing LVD (i.e., baseline PCWP > 20 mmHg), the rate of SAEs (including SAEs associated with heart failure) was significantly reduced. There were 5 SAEs among the first 24 subjects prior to the additional exclusion criterion, but only 2 SAEs among the 100 subjects[2] in the study who were enrolled and treated after the additional exclusion criterion was in place. Furthermore, there were 2 SAEs among the 4 subjects with evidence of pre-existing left ventricular dysfunction, but only 5 SAEs amongst the 120 subjects without evidence of left ventricular dysfunction. This result was unexpected and came as a great surprise to those working on the study.

18. Based upon this unexpected finding, INOT submitted a labeling supplement to FDA on February 25, 2009, seeking to amend the prescribing information for INOMAX® to include a warning statement for physicians indicating that the use of inhaled NO in patients with pre-existing LVD could cause SAEs, such as pulmonary edema. No such warning regarding pre-existing LVD was previously required to appear in the prescribing information for inhaled NO in the U.S. Following INOT's submission of the labeling supplement to FDA, FDA agreed that a warning regarding pre-existing LVD was required. On August 28, 2009, FDA approved the INOMAX® label supplement that included the following new information:

> *WARNINGS AND PRECAUTIONS*
>
> *Heart Failure: In patients with pre-existing left ventricular dysfunction, inhaled nitric oxide may increase pulmonary capillary wedge pressure leading to pulmonary edema (5.4).*

[2] In a prior declaration signed by me in a related case (and previously submitted in the present case at least once, e.g., as part of Item 14 of an Information Disclosure Statement filed on December 7, 2012), I inadvertently misstated this number as "80 subjects". See ¶ 14 of the Declaration of James S. Baldassarre, M.D., under 37 C.F.R. § 1.132 signed on September 29, 2010. The correct number is 100.

> *5 WARNINGS AND PRECAUTIONS*
>
> *5.4 Heart Failure: Patients who had pre-existing left ventricular dysfunction treated with inhaled nitric oxide, even for short durations, experienced serious adverse events (e.g., pulmonary edema).*

Thereafter, similar warnings were added to the INOmax® label in Japan, Europe, Canada and Australia.

19. In my expert opinion, prior completion of the INOT22 study and analysis of the adverse events that occurred during that study, it was not common sense to any expert in this field of medicine to exclude neonates, near-term neonates or children diagnosed with pre-existing LVD from having inhaled NO administered for diagnostic or treatment purposes, unless, of course, the subject was also known to be dependent on right-to-left shunting of blood (a contraindication on the prescribing information for INOMAX®).

20. 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 were 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 any patent that may issue on the present application.

Dated: 12/4/2013

James S. Baldassarre, M.D.

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EXHIBIT 1

JAMES S. BALDASSARRE, MD
145 Pebble Woods Dr. Doylestown, PA 18901
jbaldassarre@verizon.net
(215) 348-2835
(908) 500-8111

Executive Overview

Accomplished pharmaceutical development executive with a depth of experience in Clinical Research, international Regulatory Affairs, Medical Affairs and Pharmacovigilance across a variety of therapeutic areas. Particular expertise in the design, execution and analysis of clinical research trials within an academic or regulatory environment. Deliberate focus on quality of deliverables, personal integrity, accountability, work ethic and efficiency. Highly regarded interpersonal and communication skills, with sensitivity to culture and audience.

Professional Experience

Durata Therapeutics, Branford Ct **9/2013-present**

Executive Director, Clinical and Medical Affairs

Ikaria LLC, Hampton NJ

Vice President Global Medical Affairs **3/2012-9/2012**

- Project/Medical Leader IK 3001 (INOmax®) (neonatology and CV surgery)
- Medical Lead for Labeling Review Committee
  - Medical oversight of successful labeling revisions as part of product protection strategy
- Leadership Team member
- Medical Lead for Advertising and Promotions Review Committee
- Research Management Committee member
- Grant Support Committee (including evaluation of investigator-initiated trials)

Ikaria LLC
Vice President R&D **4/2007 to 3/2012**

- Medical Leader IK 5001, injectable device for prevention of congestive heart failure
  - In-licensed product and created development plan for highly innovative medical device, leading to FDA IDE approval
  - Lead IK 5001 Project Team
  - Created numerous development scenarios and lead team through formal decision analysis process
  - Managed relationship with Israeli partner company including quarterly Joint Development Committee meetings

- Medical Leader IK 3001 (INOmax®), prevention of BPD in premature infants
  - Lead IK 3001 Project Team

  - Designed and initiated phase 3 pivotal trial
  - Completed enrollment ahead of schedule
  - Developed innovative site communication strategy based on study extranet and HTML-based study newsletters with metrics, allowing near-real time assessment of site activity
  - Successfully submission for Pediatric Exclusivity
- Business Development Team; BD activities included preliminary and detailed due diligence on numerous compounds
  - 3 compounds successfully in-licensed
- Supervised Director of Drug Safety and two Research Directors
- Member of the Research Management Committee (RMC) with monthly review and critique of all research projects (drug and device)

INO Therapeutic, Clinton NJ

Senior Director **9/2003 to 4/2007**

- Led cross-functional team to manage life cycle for the company's flagship product
  - Designed and executed 800 subject phase 3 trial in 9 EU countries
  - Designed and executed numerous other phase 2 trials for additional indications leading to publication, selection an oversight of investigator-initiated trials, pharmacovigilance and safety review, numerous interactions with FDA including successful sNDA, and numerous Type B and Type C meetings.
  - Contributed medical input to clinical study protocols, statistical analysis plans, clinical study reports and manuscripts.
  - Wrote and revise numerous additional documents including IND annual updates, PSURs and investigational drug brochures.
- Oversaw clinical development staff of 20, including clinical operations, data management, biostatistics and pharmacovigilance
  - Created customized skills mapping tool for R&D staff development and succession planning.
- Named inventor on several additional 'method of use' patents central to successful life cycle strategy
  - Patents now issued in US, EU Australia
- Reviewed and approval promotional materials, educational materials and press releases.
- Lead negotiations with numerous independent academic and government investigators to coordinate research strategy for INOmax; including access to NIH-sponsored study data for use in FDA submissions, reanalysis of this data and preparation of reports suitable for FDA submission.
- Provided medical input to device development, design specifications and safety review and reporting

J&J Pharmaceutical Research and Development, Raritan, NJ

Compound Development Team Leader/Clinical Leader-REGRANEX® **1/2003 to 9/2003**

- Led Franchise team for marketed wound healing product based on recombinant platelet-derived growth factor.
- Led project team to successful resolution of commitments with EMEA.

Senior Director, Operations Team Management **3/2001 to 1/2003**

- Project management leadership for several project teams, with primary emphasis in oral hypoglycaemic and anti-obesity drugs.
- Applied methodologies to improve project planning, and risk and cost management.
- Assisted with implementation of pilot eDC project.

Janssen Research Foundation

Director of Clinical Research Italy/Greece/Spain et alia **8/1999-3/2001**

- Member of European R&D leadership team, reporting to EVP in Belgium.
- Managed Clinical Research staff in several countries, implementing new organization structure and processes, including country specific enrolment metrics.

Janssen-Cilag Limited, UK

Head of Clinical Research and Senior Medical Advisor **3/1997 -8/1999**

- Managed a group of 5 clinical research managers in all therapeutic areas of interest to Janssen Research Foundation, including epilepsy (Topamax), schizophrenia (Risperdal), pain (Ultram) and gastric dysmotility.
- Oversaw execution of Phase 1-4 clinical trials
- Senior Medical Advisor also reviewed and approved promotional materials, training materials, educational materials etc. Participated on the Johnson & Johnson Signature of Quality internal assessment as lead from Clinical Research, leading to J&J SoQ Bronze Award

R.W. Johnson Pharmaceutical Research Institute Spring House, PA

Associate Director, Clinical Research **1995-1997**
Assistant Director, Clinical Research **1993-1995**

Presbyterian Medical Center Philadelphia, PA

Attending Physician, Division of Infectious Diseases	**1992 – 1993**

Medical College of Pennsylvania, Philadelphia, PA

Fellow, Division of Infectious Diseases	**1990-1993**
Three-year program with 9 months bench research	
Medical Director (half time)	**1989-1990**
Internship/Residency Internal Medicine	**1986-1989**

Philadelphia Department of Health, Philadelphia, PA

Medical Director, Sexually Transmitted Diseases Clinic (half time)	**1989 - 1990**

Certifications and Appointments

Diplomat, ABIM

Internal Medicine	1989-
Infectious Diseases	1992-2002
Limited GMC Registration (UK)	1999-

Medical College of Pennsylvania

Clinical Assistant Professor of Medicine	1994-

John Radcliffe Hospital, Oxford, England

Honorary SHO, Dept of Clinical Pharmacology	1999-2000

Education

M.D.	S.U.N.Y. Downstate Medical Center, Brooklyn, NY	1986
B.S. Biology	Harpur College (S.U.N.Y.), Binghamton, NY	1982

Other Activities and Awards

RWJ-PRI Continuous Process Improvement Committee/Award	1995-1996
Johnson & Johnson Signature of Quality submission	1997, 1999
JJ PRD New Product Development Committee Implementation Team	2002-2003

Ikaria On the Spot Awards

- IK 5001 In-licensing 2010
- IK-5001 IDE submission 2011
- IK-3001 MoU patent approval 2012

Publications

1. Levison M E and Baldassarre J S: Intra-Abdominal Infections. *Current Practice of Medicine* 1993.
2. Baldassarre J S and Abrutyn E: Antibiotic-Resistant Streptococcus pneumoniae. Infectious Disease Practice 1993; 17 (9).
3. Baldassarre J S and Abrutyn E: Genital Ulcer Disease. *Infectious Disease Practice* 1992; 16 (9); 1-7.
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5. Levison M E and Baldassarre J S: Community Acquired Pneumonia: Keys to Making the Diagnosis. *Modern Med* 1992; 60: 11 42-58.
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EXHIBIT D

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.

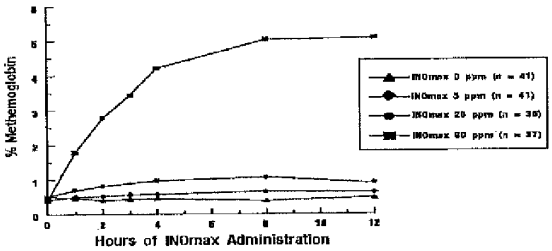
Effects on Pulmonary Vascular Tone in PPHN
Persistent pulmonary hypertension of the newborn (PPHN) occurs as a primary developmental defect or as a condition secondary to other diseases such as meconium aspiration syndrome (MAS), pneumonia, sepsis, hyaline membrane disease, congenital diaphragmatic hernia (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%)	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

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	6/89 (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

EXHIBIT E

INOmax® (nitric oxide) for inhalation

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use INOmax safely and effectively. See full prescribing information for INOmax.

INOmax (nitric oxide) for inhalation
Initial U.S. Approval: 1999

RECENT MAJOR CHANGES

Warnings and Precautions, Heart Failure (5.4) 8/2009

INDICATIONS AND USAGE

INOmax is a vasodilator, which, in conjunction with ventilatory support and other appropriate agents, is indicated for the treatment of term and near-term (>34 weeks gestation) 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 (1.1).

Monitor for PaO_2, methemoglobin, and inspired NO_2 during INOmax administration (1.1).

Utilize additional therapies to maximize oxygen delivery (1.1).

DOSAGE AND ADMINISTRATION

Dosage: The recommended dose of INOmax is 20 ppm, maintained for up to 14 days or until the underlying oxygen desaturation has resolved (2.1).

Administration:

- INOmax must be delivered via a system which does not cause generation of excessive inhaled nitrogen dioxide (2.2).
- Do not discontinue INOmax abruptly (2.2).

DOSAGE FORMS AND STRENGTHS

INOmax (nitric oxide) is a gas available in 100 ppm and 800 ppm concentrations.

CONTRAINDICATIONS

Neonates known to be dependent on right-to-left shunting of blood (4).

WARNINGS AND PRECAUTIONS

Rebound: Abrupt discontinuation of INOmax may lead to worsening oxygenation and increasing pulmonary artery pressure (5.1).

Methemoglobinemia: Methemoglobin increases with the dose of nitric oxide; following discontinuation or reduction of nitric oxide, methemoglobin levels return to baseline over a period of hours (5.2).

Elevated NO_2 Levels: NO_2 levels should be monitored (5.3).

Heart Failure: In patients with pre-existing left ventricular dysfunction, inhaled nitric oxide may increase pulmonary capillary wedge pressure leading to pulmonary edema (5.4).

ADVERSE REACTIONS

Methemoglobinemia and elevated NO_2 levels are dose dependent adverse events. Worsening oxygenation and increasing pulmonary artery pressure occur if INOmax is discontinued abruptly. Other adverse reactions that occurred in more than 5% of patients receiving INOmax in the CINRGI study were: thrombocytopenia, hypokalemia, bilirubinemia, atelectasis, and hypotension (6).

To report SUSPECTED ADVERSE REACTIONS, contact INO Therapeutics at 1-877-566-9466 and http://www.inomax.com/ or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

Nitric oxide donor agents: Nitric oxide donor compounds, such as prilocaine, sodium nitroprusside, and nitroglycerin, when administered as oral, parenteral, or topical formulations, may have an additive effect with INOmax on the risk of developing methemoglobinemia (7).

Revised: August 2009

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Treatment of Hypoxic Respiratory Failure

INOmax® is a vasodilator, which, 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.

Utilize additional therapies 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 Studies (14)]*.

Monitor for PaO_2, methemoglobin, and inspired NO_2 during INOmax administration.

2 DOSAGE AND ADMINISTRATION

2.1 Dosage

Term and near-term neonates with hypoxic respiratory failure

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.

2.2 Administration

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.

Do not discontinue INOmax 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.

3 DOSAGE FORMS AND STRENGTHS

Nitric oxide is a gas available in 100 ppm and 800 ppm concentrations.

4 CONTRAINDICATIONS

INOmax is contraindicated in the treatment of neonates known to be dependent on right-to-left shunting of blood.

5 WARNINGS AND PRECAUTIONS

5.1 Rebound

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

5.2 Methemoglobinemia

Methemoglobinemia increases with the dose of nitric oxide. In 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.

5.3 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.

5.4 Heart Failure

Patients who had pre-existing left ventricular dysfunction treated with inhaled nitric oxide, even for short durations, experienced serious adverse events (e.g., pulmonary edema).

6 ADVERSE REACTIONS

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The adverse reaction information from the clinical studies does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates.

6.1 Clinical Trials Experience

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 273 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 reactions that occurred in at least 5% of patients receiving INOmax in the CINRGI study with event rates >5% and greater than placebo event rates. None of the differences in these adverse reactions were statistically significant when inhaled nitric oxide patients were compared to patients receiving placebo.

Table 1:
Adverse Reactions in the CINRGI Study

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%)

6.2 Post-Marketing Experience

The following adverse reactions have been identified during post-approval use of INOmax. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to estimate their frequency reliably or to establish a causal relationship to drug exposure. 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.

7 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.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

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.

8.2 Labor and Delivery

The effect of INOmax on labor and delivery in humans is unknown.

8.3 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.

8.4 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.

8.5 Geriatric Use

Nitric oxide is not indicated for use in the adult population.

10 OVERDOSAGE

Overdosage with INOmax will be manifest by elevations in methemoglobin and pulmonary toxicities associated with inspired 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.

11 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:

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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 selectively dilates the pulmonary vasculature, and because of efficient scavenging by hemoglobin, has minimal effect on the systemic vasculature.

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.

12.2 Pharmacodynamics

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).

12.3 Pharmacokinetics

The pharmacokinetics of nitric oxide has been studied in adults.

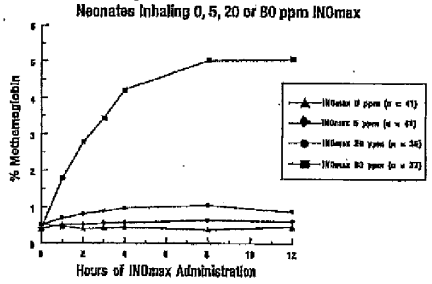
12.4 Pharmacokinetics: Uptake and Distribution

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.

12.5 Pharmacokinetics: 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.

12.6 Pharmacokinetics: 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.

13 NONCLINICAL TOXICOLOGY

13.1 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.

14 CLINICAL STUDIES

14.1 Treatment of Hypoxic Respiratory Failure (HRF)

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 × fraction of inspired oxygen concentration [FiO_2]× 100 divided by systemic arterial concentration in mm Hg [PaO_2]) and increases PaO_2 *[see Clinical Pharmacology (12.1)]*.

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 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

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 (6.1)]*. 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 3.

Table 3:
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 (6.1)]*.

14.2 Ineffective in Adult Respiratory Distress Syndrome (ARDS)

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.

16 HOW SUPPLIED/STORAGE AND HANDLING

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.

INO Therapeutics
6 Route 173 West
Clinton, NJ 08809
USA

EXHIBIT F

CLINICAL FEATURES

Clinical features of PH are:
1. Symptoms: dyspnea, substernal chest pain, fatigue, syncope
2. Physical signs: loud P_2, tricuspid insufficiency murmur, prominent parasternal (right ventricular) impulse, right-sided S_4; also, right-sided S_3, jugular venous distention, peripheral edema in the case of right ventricular failure

Although the overall constellation of symptoms in patients with PH depends on the underlying disease, certain characteristic complaints can be attributed to the PH itself. Dyspnea on exertion and fatigue are frequently observed in all forms of PH, even in the absence of any gas exchange abnormalities. The mechanism of the dyspnea is likely due to activation of stretch receptors in the pulmonary arteries and right ventricle, which are stimulated as cardiac output increases with exertion. In patients with PH related to underlying parenchymal lung disease, it is often difficult to know how much of the dyspnea is due to the PH as opposed to the underlying lung disease. Cardiopulmonary exercise testing may be useful in partitioning the relative contributions of each to dyspnea. Patients may have substernal chest pain that is difficult if not impossible to distinguish from classic angina pectoris, particularly because the pain is frequently precipitated by exertion. In most instances, the chest pain is presumed to be related to the increased workload of the right ventricle and to right ventricular ischemia, although in some cases an enlarged pulmonary artery can compress the left main coronary artery and produce true left ventricular ischemia. When PH is severe and the right ventricle is failing, patients are unable to increase cardiac output with exertion and may experience exertional lightheadedness or frank syncope. These are very poor prognostic signs.

Physical examination shows several features more related to the cardiac consequences of PH than to actual disease of pulmonary vessels. PH itself does not cause any changes that can be noted on examination of the lungs, although patients with underlying lung disease often have findings related to their primary disease. On cardiac examination, patients frequently exhibit an accentuation of the pulmonic component of the second heart sound (P_2) because of earlier and more forceful valve closure attributable to high pressure in the pulmonary artery. A murmur of tricuspid insufficiency is commonly heard, and a pulmonic insufficiency (Graham Steell) murmur may be appreciated. When the pulmonary artery is enlarged, a pulsation may be felt at the left upper sternal border (pulmonary artery tap). With right ventricular hypertrophy, there is often a prominent lift or heave of the region immediately to the left of the lower sternum, corresponding to a prominent right ventricular impulse during systole. As the right atrium contracts and empties its contents into the poorly compliant, hypertrophied right ventricle, a presystolic gallop (S_4) originating from the right ventricle may be heard. When the right ventricle fails, a mid-diastolic gallop (S_3) in the parasternal region is frequently heard, and the jugular veins become distended. At this stage, both lower extremity peripheral edema and ascites may develop.

DIAGNOSTIC FEATURES

Echocardiography is usually the first test to suggest a diagnosis of PH. Key findings are right ventricular hypertrophy and elevated right ventricular systolic pressure by Doppler estimates. Detailed description of these echocardiographic techniques is beyond the scope of this chapter but can be found in standard cardiology textbooks.

Definitive diagnosis of PH and precise quantification of its hemodynamics require cardiac catheterization. Measurements of right ventricular, pulmonary arterial, and pulmonary capillary wedge pressures are important in confirming the diagnosis, determining disease severity, and assessing the response to acute vasodilator testing to guide the patient's subsequent management (see Chapter 12 for discussion of pulmonary artery catheterization).

Clues to the status of the pulmonary vessels can be provided by chest radiography in some patients. With mild PH originating at the arterial or arteriolar level, frequently no abnormalities are seen. As PAH becomes more significant, the central (hilar)

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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 13/683,236	Filing Date 11/21/2012	☐ To be Mailed

ENTITY: ☒ LARGE ☐ SMALL ☐ MICRO

APPLICATION AS FILED – PART I

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

APPLICATION AS AMENDED – PART II

AMENDMENT	12/23/2013	(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))	* 15	Minus	** 30	= 0	X $80 =	0
	Independent (37 CFR 1.16(h))	* 4	Minus	***4	= 0	X $420 =	0
	☐ Application Size Fee (37 CFR 1.16(s))						
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
						TOTAL ADD'L FEE	**0**

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

LIE
/Tina J. Barden/

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Doc Code: TRACK1.GRANT

Decision Granting Request for Prioritized Examination (Track I or After RCE)	Application No.: 13/683,236

1. THE REQUEST FILED December 23, 2013 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)

U.S. Patent and Trademark Office
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Doc Code: TRACK1.GRANT

CORRECTED Decision Granting Request for Prioritized Examination (Track I or After RCE)	Application No.: 13/683,236

1. THE REQUEST FILED December 23, 2013 IS **GRANTED.**

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

A. ☐ for an original nonprovisional application (Track I).
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/Brian W. Brown/
[*Signature*]

Petitions Examiner, Office of Petitions
(Title)

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/683,236	11/21/2012	James S. Baldassarre	26047-0003006	5655

94169 7590 02/05/2014

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EXAMINER	
ARNOLD, ERNST V	
ART UNIT	PAPER NUMBER
1613	
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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. 13/683,236	Applicant(s) BALDASSARRE, JAMES S.	
	Examiner ERNST ARNOLD	Art Unit 1613	AIA (First Inventor to File) Status No

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

Period for Reply

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

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

Status

1)☒ Responsive to communication(s) filed on *12/23/13*.

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

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

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

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

Disposition of Claims*

5)☒ Claim(s) *1,6-10,21,25,26 and 31-36* 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) *1,6-10,21,25,26 and 31-36* is/are rejected.

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

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

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

Application Papers

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

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

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

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

Priority under 35 U.S.C. § 119

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

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

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

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

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

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

Attachment(s)

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

2) ☒ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date *12/23/13*.

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

4) ☐ Other: _____.

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

DETAILED ACTION

A request for continued examination under 37 CFR 1.114 was filed in this application after appeal to the Patent Trial and Appeal Board, but prior to a decision on the appeal. 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, the appeal has been withdrawn pursuant to 37 CFR 1.114 and prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on 12/23/13 has been entered.

Claims 33-36 are new. Claims 3-5, 11-20, 22-24 and 27-30 have been cancelled. Claims 1, 6-10, 21, 25, 26 and 31-36 are pending and under examination.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on 12/23/13 was filed after the mailing date of the office action on 4/24/13. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Priority

Applicant has amended the independent claims 1, 21, 33 and 35 to include the recitations of "providing a pharmaceutical product" and in claims 1 and 21 "generating a cylinder containing compressed nitric oxide gas...". The priority documents disclose methods of “providing pharmaceutically acceptable nitric oxide gas” (See claims 16 and 20 of 12/494598, for example) but do not disclose providing any pharmaceutical product but only nitric oxide gas. Furthermore, 12494598 teaches with respect to the gas cylinder:

> [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

The question is whether having a compressed cylinder of NO and nitrogen in hand the same as the method step of “generating a cylinder….”? After consultation with two Supervisory Examiners, it is the position of the Office that "generating a cylinder containing compressed nitric oxide gas..." is also not supported in the priority document for the following reasons. First of all, ‘generating’ the cylinder was not contemplated in the earlier filed document. The plain and ordinary meaning of ‘generate’ is to produce something; to bring into existence. At most the priority document suggests that one would obtain or be supplied with the pre-manufactured cylinder but it does not extrapolate that one can ‘generate’, ie., bring into existence, the cylinder. Bringing something into existence is a different concept from obtaining a previously made product and is not previously contemplated in the priority document.

Additionally, independent claims 1, 21, 33 and 35 all recite providing first and second warnings which concept cannot be found in the priority documents. Thus, as a whole the instantly claimed subject matter was not present in the priority documents.

Consequently, for application of prior art, Applicant is only afforded the filing date of the instant application which is 11/21/12.

The Declaration filed on 12/23/13 under 37 CFR 1.131(a) has been considered but is ineffective to overcome the VasoKINOX reference. The VasoKINOX reference is a statutory bar under pre-AIA 35 U.S.C. 102(b) and thus cannot be overcome by an affidavit or declaration under 37 CFR 1.131(a).

Withdrawn rejections:

Applicant's Declarations, amendments and arguments filed 12/23/13 are acknowledged and have been fully considered. The Examiner has re-weighed all the evidence of record. Any rejection and/or objection not specifically addressed below is herein withdrawn.

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

Claim Rejections - 35 USC § 103

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

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

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

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

Claims 1, 6-10, 21, 25, 26 and 31-36 are rejected under 35 U.S.C. 103(a) as being unpatentable over VasoKINOX (IDS filed 4/12/13; 07/2008, 37 pages) and NEJM (NEJM 1997; 336(9):597-604) and Kazerooni et al. (Cardiopulmonary Imaging 2004, Lippincott Williams & Wilkins, pages 234 and 236 in part) and Loh et al. (Circulation 1994, 90, 2780-2785) and Leo (Primary Care Companion J Clin Psychiatry 1999, 1:5; pp 131-141) and Himashree et al. (Current Science 2003, 85, 5, pages 607-614) and McLaughlin et al. (Circulation, 2006, 114, 1417-1431) and Smyth (Thorax 2000;55(suppl 1):S51-S55) and Burkhoff et al. (Am J Physiol 1993, 34:H1819-H1828) and Fromm et al. (The Journal of Emergency Medicine 1995, 13(1):71-87) and Bernasconi et al. (Images Paediatr Cardiol; 2002, 4(1):4-29).

Applicant claims a method of providing a pharmaceutical product.

Determination of the scope and content of the prior art

(MPEP 2141.01)

VasoKINOX teaches methods of providing the pharmaceutical product VasoKINOX (pages 19-21 of 37) by supplying a cylinder of mixed nitrogen/nitric oxide under a pressure of 200 bar (pages 21, 23, 33 and 36 of 37) and other devices such as ventilators (page 24 of 37) and treating pulmonary hypertension, which is coextensive with hypoxic respiratory failure and a condition for which inhaled nitric oxide is indicated, via inhaled nitric oxide gas from a cylinder in adults and children with a mean pulmonary arterial pressure to mean systemic pressure ratio greater than or equal to 50% and/or pulmonary vascular resistance greater than or equal to 5 UWood (pages 23 and 32 of 37) with the warnings/prescribing information to not use VasoKINOX in the event of these distinct contraindications/warnings:

- Left ventricular dysfunction (LVD);
- All forms of pulmonary arterial hypertension due to pulmonary hyper-flow; and
- Newborns dependent on a right-to-left shunt (first warning) or with a malignant left-right arterial canal (pages 25 and 32 of 37). Newborns read on neonatal patients.

VasokINOX also warns that treatment with iNO might aggravate cardiac insufficiency in a situation with left-to-right shunting (Page 25 of 37, 4.4). Thus, the artisan in the art of iNO is well aware to determine if the first neonate patient has pre-existing LVD and that the artisan is aware that right to left shunting or left to right arterial canals are contraindicated when administering iNO. Additionally, the artisan is aware

that patients which are not dependent on right to left shunting of blood are not contraindicated and are thus candidates for iNO treatment. VasoKINOX teaches dosage determined by the doctor considering the patient's clinical condition and age and recommendations of 20 ppm NO after dilution in an air/oxygen mixture (page 23 (4.2) and 34 of 37, bottom) from cylinder of mixed nitrogen/nitric oxide under a high pressure of 200 bar (pages 21, 23, 33 and 36 of 37) and is marketed by AIR LIQUIDE (pages 20, 31 and 37 of 37). Note that the dosage recommendations appears in the same prescribing document with the warnings that is supplied to the medical provider which the Examiner interprets that the warnings/prescribing information comes with the source of the nitric oxide gas. VasoKINOX warns of pulmonary edema (pages 27 and 35 of 37). VasoKINOX teaches how to transport the cylinders (page 30 of 37).

VasoKINOX teaches that NO is a vasodilator and reduces pulmonary vascular resistance which implicitly can create vascular hypotension (page 28 of 37).

Consequently, it is implicit in the disclosure of VasoKINOX for the medical provider to evaluate/make the decision on a case by case basis for the potential benefit of treating the patient with 20 ppm inhaled NO for the potential benefit vs. the potential risk of the warnings prior to treatment with inhaled nitric oxide and exclude any number of newborns who meet the exclusion criteria and thus avoid the risk of putting one or more of these patients at risk of pulmonary edema and administer VasoKINOX to any number of patients including newborns who pass the exclusion criteria. The only way to determine if the patient meets the exclusion criteria is to perform at least one diagnostic test to ascertain if the condition is present. In other words, if the newborn is not

dependent on right to left shunting of blood and does not have LVD then the medical provider makes the decision to treat the newborn with 20 ppm inhaled NO. It is also implicit that the nitric oxide gas source was generated prior to supplying to the medical provider by being compressing under high pressure a mixture of nitric oxide and nitrogen gases into the cylinder otherwise one would not have a compressed gas cylinder generated for the medical provider.

Bernasconi et al. is directed to iNO applications in paediatric practice (title) and discusses iNO treatment of neonates with hypoxaemic respiratory failure is well known in the art (pages 7-9 of 25). Bernasconi et al. warn of the negative effects of inhaled NO in patients with left ventricular dysfunction leading to pulmonary edema with corresponding rationale (page 6 of 25) and teaches that these factors highlight the need for careful observation and intensive monitoring during NO inhalation in patients with left ventricular failure (page 7 of 25). Thus even general reviews of the art linked iNO treatment of paediatric patients with the risk of pulmonary edema when LVD is present so the ordinary artisan is well aware of this risk.

Kazerooni et al. teach that PCWP is used to reflect left-sided heart function and is a reflection of left ventricular dysfunction (page 234). Kazerooni et al. teach that normal PCWP is 6-12 mm Hg and as the PCWP rises to 18-25 mm Hg, it exceeds the normal colloid osmotic pressure of blood and a fluid transudate develops in the lung interstitium edema which is the instantly claimed second warning (page 236). Also note that Applicant teaches that normal upper limit of PCWP in children is 10-12 mm Hg and

in adults is 15 mm Hg [0060]. Therefore the ordinary artisan in the cardiac field knows very well that a PCWP of greater than 20 mm Hg results in edema.

Smyth teaches iNO treatment for preterm infants (neonates) with hypoxic respiratory failure (title, abstract and S54 learning points, for example).

NEJM teaches treatment of neonates with hypoxic respiratory failure with 20 ppm iNO (Abstract and Table 4) and that hypoxic respiratory failure was caused by persistent pulmonary hypertension (page 598, patients; Tables 1 and 5) with 78% having evidence for pulmonary hypertension (page 599, right column). Since not all the neoates had right-to-left shunting of blood, then it is implicit that the neonates with hypoxic respiratory failure include some who do not have LVD and who are not dependent on right-to-left shunting of blood. Thus, the ordinary artisan in the art of iNO understands that hypoxic respiratory failure and pulmonary hypertension are coextensive and the treatment is 20 ppm iNO.

Loh et al. teach that inhalation of nitric oxide in patients with LVD can increase the pulmonary artery wedge pressure (synonymous with PCWP) as measured by echocardiography (Abstract and Figure 2 and page 2782 right column). Loh et al. teach that the more severe LV dysfunction was present in the patients who had the largest increases in pulmonary artery wedge pressure with inhaled NO (bottom right column page 2782). Indeed, Loh et al. defined a group of patients with a pulmonary artery wedge pressure of ≥18 mm Hg indicating LV failure had a greater effect of inhaled NO (page 2784, left column).

Himashree et al. teach INO for persistent pulmonary hypertension of the newborn and that adverse effects of inhaled NO include systemic hypotension and methaemoglobinemia and that infants "who receive INO therapy should be monitored according to protocols designed to avoid the potential toxic effects associated with INO administration" (Abstract and pages 610-611, Adverse effects of INO).

Leo teaches that primary care physicians can make treatment decisions based on assessment of benefits and risks as shown in Table 1 (page 133) below:

Table 1. Standards for Capacity Assessment as a Function of Patient Decision and Benefits/Risks Associated With an Intervention[a]

	Intervention	
Decision	Likely Beneficial Outcome and/or Low Risk	Likely Poor Outcome and/or High Risk
Accept intervention	Low standard for capacity assessment	High standard for capacity assessment
Refuse intervention	High standard for capacity assessment	Low standard for capacity assessment

[a]Adapted from Roth et al.[3]

Leo teaches understanding the natural course of the Medical condition; understanding the proposed treatment intervention; understanding the risks and potential benefits; understanding the consequences of treatment or intervention refusal and understanding viable alternatives (page 135).

McLaughlin et al. teach that pulmonary hypertension can be caused associated with left ventricular heart disease (Table 1) and that edema is a symptom of pulmonary arterial hypertension (PAH) (Table 2, page 1420). McLaughlin et al. teach that pulmonary hypertension in hypoxic states is well recognized (left column page 1421 and left column page 1429). McLaughlin et al. also teach a diagnostic algorithm using, for

example, an echocardiogram determination of left heart disease and that Doppler echocardiography is the essential screening tool for the presence of PAH. (Figure 3, page 1422, right column and page 1423, Figure 4C).

Fromm et al. teach pulmonary edema is caused by congestive heart failure which includes left ventricular dysfunction and impaired ejection of the left ventrical leads to increased pulmonary vascular pressures (Introduction, Historical Background, Etiology, Figure 1, Pathophysiology). Fromm et al. teach that it is a law of physiology that pulmonary edema is related to hydrostatic pressure gradient between the capillary and the interstitium of the lung and occurs when the net flow of fluid from the capillaries into the lung exceeds the capacity of the pulmonary lymphatics (pages 76, bottom right through page 77 top left). Fromm et al. teach that given the physiological derangements in CHF, the use of vasodilating agents to improve cardiac output and survival is only logical (page 81, left column).

Burkhoff et al. teach that it is well known that one of the most important consequences of left ventricular dysfunction is pulmonary edema (Abstract).

Summary of the preponderance of factual evidence:

- ‘generating' cylinders of nitric oxide gas by compressing nitric oxide gas and nitrogen gas under high pressure and providing prescribing dose recommendation information is well known in the art;
- Supplying cylinders of nitric oxide gas to medical providers for treating neonates with hypoxic respiratory failure who do not have LVD and who

are not dependent on right-to-left shunting of blood with a recommended dose of 20 ppm NO is well known in the art;

- Providing a warning to the medical provider that iNO is contraindicated in the treatment of neonates dependent on right-to-left shunting of blood is already taught in the art;
- iNO is known to cause pulmonary edema in patients with LVD;
- iNO is known to increase PCWP and it is well known that an increase in PCWP can lead to pulmonary edema and consequently there is a risk of pulmonary edema from the administration of iNO;
- it is also very well known in the art that impaired ejection of the left ventricle, hence left ventricular dysfunction, leads to increased pulmonary vascular pressures and pulmonary edema and consequently patients with left ventricular dysfunction, which is necessarily pre-exisiting, are at risk of pulmonary edema; and
- it is well known in the art that primary care physicians can make treatment decisions based on assessment of benefits and risks and understanding the natural course of the Medical condition; understanding the proposed treatment intervention; understanding the risks and potential benefits; understanding the consequences of treatment or intervention refusal and understanding viable alternatives.

Ascertainment of the difference between the prior art and the claims

(MPEP 2141.02)

1. The difference between the instant application and the cited art is that cited art does not expressly teach generating the cylinder of NO gas; that neonates with hypoxic respiratory failure include some who do not have LVD and who are not dependent on right-to-left shunting of blood and that inhaled NO may/could increase PCWP leading to a potential risk of pulmonary edema. This deficiency in the cited art is cured by the combined teachings of VasoKINOX, Kazerooni et al., Smyth, NEJM, Fromm et al., Burkhoff et al., Bernasconi et al., McLaughlin et al. and Loh et al.

2. The difference between the instant application and the cited art is that cited art does not expressly teach evaluating on a case-by-case basis determining if the potential benefit of the treatment outweighs the potential risk described in the second warning and treating the patient with LVD with 20 ppm iNO or discontinuing treatment with iNO if pulmonary edema occurs and make a decision whether or not to treat the first patient that has LVD or a second patient with hypoxic respiratory failure but without LVD and not dependent on right to left shunting of blood. This deficiency in cited art is cured by the teachings of VasoKINOX, Bernasconi et al., Kazerooni et al., Smyth, NEJM, Fromm et al., Burkhoff et al., Loh et al. and of Leo.

3. The difference between the instant application and the cited art is that the cited art is that cited art does not expressly teach performing echocardiography to identify a neonate who is a candidate for iNO treatment and discontinuing treatment due to

hypotension or monitoring for evidence of an increase in PCWP or pulmonary edema during treatment. This deficiency in cited art is cured by the combined teachings of VasoKINOX, Bernasconi et al., Kazerooni et al., Smyth, NEJM, Loh et al., Fromm et al., Burkhoff et al., and Leo and Himashree et al. and McLaughlin et al.

4. The difference between the instant application and the cited art is that cited art does not expressly teach the exact sequence of steps found in claims 33-36. This deficiency in the cited art is cured by the combined teachings of VasoKINOX, Bernasconi et al., Kazerooni et al., Smyth, NEJM, Fromm et al., Burkhoff et al. and Loh et al. and Leo and Himashree et al. and McLaughlin et al.

Finding of prima facie obviousness

Rational and Motivation (MPEP 2142-2143)

1. It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to perform the methods of VasoKINOX and Smyth and NEJM and Bernasconi et al. on neonates with hypoxic respiratory failure where the neonates with hypoxic respiratory failure include some who do not have LVD and who are not dependent on right-to-left shunting of blood and teach that inhaled NO may/could increase PCWP leading to a potential risk of pulmonary edema**,** as suggested by Kazerooni et al., Smyth, NEJM, Fromm et al., Burkhoff et al. and Loh et al. and generate a cylinder of NO gas and produce the instant invention.

One of ordinary skill in the art would have been motivated to do this because it is well known in the art to treat pulmonary hypertension as well as neonatal hypoxic respiratory failure with iNO no matter the cause of the pulmonary hypertension/hypoxic respiratory failure including neonates not dependent on right to left shunting of blood and it is implicit that the patients must be identified by some diagnostic method to determine the condition. The person having ordinary skill in the art to which the claimed subject matter pertains would, of necessity have the capability of understanding the scientific and engineering principles applicable to the pertinent art. Obviously the cylinder of NO gas has to be generated by some entity to fit the specifications of VasoKINOX otherwise one could not obtain it. Applicant did not invent neonates with hypoxic respiratory failure who do not have LVD and who are not dependent on right-to-left shunting of blood. Also, it is very well known in the art that a PCWP of greater than 20 mm Hg results in edema regardless of how the PCWP is increases and it is also very well known in the art that inhaled NO increases PCWP as taught by Loh et al. Therefore is obvious to teach/warn/instruct the artisan administering iNO therapy that inhaled NO may/could increase PCWP leading to a potential risk of pulmonary edema. Placing warnings and dose recommendations on the prescribing information is already known and thus just judicious selection of the all required warnings, including first and second warnings, and dose recommendations to place in the prescribing information for the medical providers benefit is obvious. Thus, the prior art renders obvious the instantly claimed method of providing a pharmaceutical product by generating a cylinder containing compressed nitric oxide gas by a process comprising compressing nitric

oxide and nitrogen gases under high pressure; supplying a source of nitric oxide gas to a medical provider responsible for treating a plurality of neonates with hypoxic respiratory failure, including some who do not have LVD and who are not dependent on right-to-left shunting of blood; informing the medical provider that a recommended dose of inhaled nitric oxide gas for treatment of neonates with hypoxic respiratory failure is 20 ppm nitric oxide; providing a first warning to the medical provider that inhaled nitric oxide is contraindicated in the treatment of neonates dependent on right-to-left shunting of blood; and providing a second warning to the medical provider, distinct from the first warning, that in patients with pre-existing left ventricular dysfunction, inhaled nitric oxide may increase pulmonary capillary wedge pressure (PCWP) leading to pulmonary edema, the second warning being sufficient to cause a medical provider considering inhaled nitric oxide treatment for a plurality of neonatal patients who (a) are suffering from a condition for which inhaled nitric oxide is indicated, and (b) have pre-existing left ventricular dysfunction, to elect to avoid treating one or more of the plurality of patients with inhaled nitric oxide in order to avoid putting the one or more patients at risk of pulmonary edema and supplying a cylinder containing compressed nitric oxide gas to a medical provider responsible for treating a plurality of neonates with hypoxic respiratory failure, including some who do not have pre-existing LVD and who are not dependent on right-to-left shunting of blood; informing the medical provider that a recommended dose of inhaled nitric oxide gas for treatment of neonates with hypoxic respiratory failure is 20 ppm nitric oxide; providing a first warning to the medical provider that inhaled nitric oxide is contraindicated in the treatment of neonates dependent on right-to-left

shunting of blood; providing a second warning to the medical provider, distinct from the first warning, stating that patients who have pre-existing left ventricular dysfunction and are treated with inhaled nitric oxide may experience pulmonary edema, and recommending that, if pulmonary edema occurs in a patient who has pre-existing left ventricular dysfunction and is treated with inhaled nitric oxide, the treatment with inhaled nitric oxide should be discontinued. This is all simply common sense based on the preponderance of evidence by the ordinary artisan in the art.

2. It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to perform the method of methods of VasoKINOX and Smyth and NEJM and Bernasconi et al. by evaluating on a case-by-case basis and performing at least one diagnostic test to identify a neonate who has hypoxic respiratory failure but not dependent on right-to-left shunting of blood and determine that the neonate patient has pre-existing LVD**,** and determine if the potential benefit of the treatment outweighs the potential risk and make a decision whether or not to treat the first patient that has LVD or a second patient with hypoxic respiratory failure but without LVD and not dependent on right to left shunting of blood, as suggested by Kazerooni et al., Fromm et al., Burkhoff et al., Loh et al., McLaughlin et al. and Leo, and produce the instant invention.

One of ordinary skill in the art would have been motivated to do this because it is common in the medical arts for the artisan administering the therapy to make benefit/risk assessments on a case by case basis. Patients where the therapy is contraindicated by the provider of the pharmaceutical product but left with no further

options except death may have benefit from administration of iNO. This is a choice by the artisan and perfectly within the realm of an obvious decision by the artisan including the decision to terminate treatment at any time for any reason including if pulmonary edema occurs especially when the art warns of pulmonary edema as a potential adverse event. In the event that Applicant should take the position that the artisan would not administer the iNO to neonatal patients that meet the exclusion criteria of VasoKINOX, have left ventricular dysfuction consistent with a PCWP of greater than or equal to 20 mm Hg, because VasoKINOX teaches not to use the product under those conditions (left ventricular dysfuction/all forms of pulmonary arterial hypertension), it is the Examiner's position that the artisan in this art is not an automaton (See MPEP 2141.03) and in terms of the patients welfare administration of a therapy is a decision for the medical artisan and the family of the patient to determine and not the provider of the pharmaceutical product. The provider may make warnings but the medical artisan and the family of the patient may or may not abide by them depending on the risks and benefits and outcomes for the patient. Consequently, the medical practitioner may make the choice to disregard such warnings when the situation presents itself for the sake of the patient and not the distributer of the pharmaceutical product.

3. It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to perform the methods of VasoKINOX and Smyth and NEJM and Bernasconi et al. by performing performing at least one diagnostic test to identify a neonate who has hypoxic respiratory failure but not dependent on right-to-left shunting of blood and determine that the neonate patient has pre-existing LVD, as

suggested by Kazerooni et al., Fromm et al., Burkhoff et al., and Loh et al., Leo, McLaughlin et al. and Himashree et al., and produce the instant invention.

One of ordinary skill in the art would have been motivated to do this because at least Bernasconi et al. warns of pulmonary edema as an adverse event from iNO therapy in paediatric patients with left ventricular dysfunction and as taught by Loh et al. and McLaughlin et al., echocardiography is an essential diagnostic screening tool to assess the patient for left ventricular function, an exclusion criteria in the method of VasoKINOX, and Himashree et al. direct the artisan to monitor the patient for adverse events such as systemic hypotension and, as taught by Kazerooni et al. and Loh et al. and increase in PCWP over 20 mm Hg which would be indicative of edema which is a symptom of PAH as taught by Mclaughlin et al. and thus the ordinary artisan would be cognizant of this adverse event and monitor for it in at least one patient. Thus, it is obvious for the artisan to monitor for edema, hypotension and any other possible adverse event due to the administration of iNO for the patient's benefit and discontinue treatment due to the patient's hypotension or any other adverse event that places the patient's safety at risk. This is just common sense.

4. It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to perform the methods of VasoKINOX and Smyth and NEJM, Bernasconi et al. and perform all the supplying, informing, providing first warnings, providing second warnings, performing at least one diagnostic process, determining, evaluating potential benefits, identifying second neonatal patients and treating the second patient or supplying, informing, providing first warnings, providing

second warnings, performing at least one diagnostic process, determining whether or not each patient has pre-existing LVD, determining a first patient does not have LVD, treating the first patient with iNO, determining other patients do have LVD and evaluating on a case-by case basis the potential benefit vs risk of treatment, determining for at least one patient that has pre-existing LVD that the benefit outweighs the potential risk and treat the patient of instant claims 33-35 as suggested by Kazerooni et al., Fromm et al., Burkhoff et al., and Loh et al., Leo, McLaughlin et al. and Himashree et al., and produce the instant invention.

One of ordinary skill in the art would have been motivated to do this because that is what medical providers do as explained in great detail above. The instant claims are nothing more than a long winded narrative of typical medical protocol in the treatment of neonatal patients with inhaled nitric oxide that is already fully taught and suggested by the prior art and at the discretion of the medical provider to make these purely mental decisions dependent on human intelligence alone as to whether the benefits outweigh the risks of treatment for the treatment of patients with or without LVD. Indeed, VasoKINOX teaches dosage determined by the doctor considering the patient's clinical condition such as severity of pulmonary arterial hypertension and age (pages 23 (4.2) and 34 of 37) which clearly teaches and suggests evaluation of the patient's condition. Selection of patients for treatment by iNO is at the discretion of the medical provider based upon the decisions of the medical provider on a case by case basis as to whether patients with or without pre-existing LVD are provided treatment and the medical provider is fully aware that iNO may increase PCWP which leads to pulmonary edema.

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

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

Response to Arguments:

Applicant's asserts that VasoKINOX is not available as prior art against the present claims. This is incorrect because, as explained in greater detail above, the VasoKINOX reference is a statutory bar under pre-AIA 35 U.S.C. 102(b) and thus cannot be overcome by an affidavit or declaration under 37 CFR 1.131(a).

Applicant has filed 40 pages of Remarks not including 3 Declarations. Let the Examiner set the tone for the rest of the response by unequivocally stating that the Examiner strongly disagrees with each and every assertion, argument and conclusion presented by Applicant that the instantly claimed subject matter is non-obvious because the preponderance of evidence for obviousness far outweighs the evidence for non-obvious.

Applicant asserts that the Examiner has misconstrued many of the teachings in the cited art and has "problematic interpretations of the prior art's teachings". Applicant submits that the Examiner's assumptions are not accurate. Applicant asserts that

pulmonary hypertension is not a form of hypoxic respiratory failure as alleged by the Office and points to the Declaration by Dr. Greene. This is not persuasive. The Examiner notes that the claims must be given their broadest reasonable interpretation in light of the specification and Applicant clearly states that neonates having hypoxic respiratory failure associated with pulmonary hypertension [0002] which supports the Examiner's first interpretation that pulmonary hypertension is coextensive with hypoxic respiratory failure and thus the two are interrelated. Clearly, the two go hand in hand and the Examiner's interpretation remains sound. Additionally, the Examiner has supplied the reference of Smyth and NEJM which clearly teaches the specific treatment of neonates with hypoxic respiratory failure with iNO. This is all well known in the art and the rejection is over the combination of references as to what was known by the artisan. Rather it is Applicant's logic that VasoKINOX use is for iNO to treat perioperative and postoperative pulmonary hypertension in the context of cardiac surgery that is unsound because the instant claims do not exclude perioperative and postoperative pulmonary hypertension in the context of cardiac surgery and the rejection is over a combination of references and not read in a vacuum. Applicant's argument is not persuasive.

Applicant then asserts that the Office has used hindsight for LVD as a contraindication. This is incorrect because LVD is clearly printed by VasoKINOX on page 25 of 37.

4.3 Contraindications

- Left ventricular dysfunction

Applicant asserts that VasoKINOX does not provide any rationale or data that one of skill in the art could interpret as a reason why this medically important use in LVD patients should cease. This is irrelevant. The fact of the matter is that the reference clearly and unambiguously teaches LVD as a contraindication.

Applicant opines that the containdication are only applied solely for adult LVD patients and not neonates. That is mere speculation by Applicant and the reference does not differentiate the LVD for adults or children or newborns and thus it applies to all patients. Applicant's arguments are not persuasive.

Applicant asserts that the FDA did not require such a contraindication or warning in the prescribing information for INOmax® or that the INOT22 study did not exclude patients with LVD. That is irrelevant as the primary reference is VasoKINOX and they do provide a contraindication.

Applicant asserts other theoretically possible and plausible interpretations. This argument is not persuasive because the Examiner's only works with facts and not "theoretically possible interpretations" or "plausible interpretations" and the facts of the case are that the primary reference teaches treating newborns with iNO and LVD is contraindicated.

Applicant asserts that VasoKINOX does not suggest any link between contraindication for LVD and pulmonary edema. This is incorrect because VasoKINOX

does positively recite that cases of pulmonary edema have been reported after administration of high concentrations of iNO (page 27, (4.9). And the secondary references supply that information linking LVD to pulmonary edema as discussed in greater detail above by Kazerooni. Kazerooni et al. teach that PCWP is used to reflect left-sided heart function and is a reflection of left ventricular dysfunction (page 234). Kazerooni et al. teach that normal PCWP is 6-12 mm Hg and as the PCWP rises to 18-25 mm Hg, it exceeds the normal colloid osmotic pressure of blood and a fluid transudate develops in the lung interstitium edema which is the instantly claimed second warning (page 236). Thus, it is clear to the ordinary artisan that a rise in PCWP to the range above results in pulmonary edema. It is noteworthy that Applicant uses only 3 lines of text on the entire Kazerooni reference but writes almost 3 pages on other citations for this teaching which are misleading.

The other secondary references are relied upon as described by the Examiner above. With regard to Himashree et al., Applicant asserts that the Office Action fails to note several toxic effects of gas in infants and pulmonary edema is not one of them. Himashree et al. is not relied upon for that teaching as Kazerooni makes it crystal clear that a rise in PCWP above the norm results in pulmonary edema.

Applicant asserts that the edema in McLaughlin et al. is not pulmonary edema but peripheral edema and requests clarification of Table 2. Certainly McLaughlin et al. teach edema as a symptom of PAH in Table 2 and the Examiner is relying on Kazerooni for teaching that an increase in PCWP can produce pulmonary edema.

Applicant asserts that VasoKINOX does not teach:

- **Informing the medical provider that inhaled nitric oxide can be used to treat neonates with hypoxic respiratory failure.**

Applicant asserts that pulmonary hypertension is not a form of hypoxic respiratory failure. This argument and the other cited bullet points are not persuasive because the Examiner has shown that pulmonary hypertension is a form of hypoxic respiratory failure and has been addressed in detail above. Additionally, the secondary references render it obvious to treat neonates with hypoxic respiratory failure with 20 ppm of iNO. This is well known in the art.

Applicant asserts that VasoKINOX does not specify that the LVD is "pre-existing". This is absurd. It must be pre-existing in order to be diagnosed.

Applicant again comments on the contraindications. This argument was soundly rejected above.

Applicant disagrees that any deficiency in VasoKINOX is cured by any of the cited secondary references. This argument is not persuasive. MPEP 2141 states: “The proper analysis is whether the claimed invention would have been obvious to one of ordinary skill in the art after consideration of all the facts.” Also from MPEP 2141: “The prior art reference (or references when combined) need not teach or suggest all the claim limitations…” Furthermore, MPEP 2143 states: “Office personnel may properly rely on intangible realities such as common sense and ordinary ingenuity.” Thus, the instantly claimed subject matter as a whole, in light of the preponderance of evidence, is obvious to the artisan in the medical arts as it requires no ingenuity to treat or not treat a neonatal patient with or without LVD with iNO as instantly claimed. This is a decision

made by the artisan on case-by-case basis as described in detail above. This argument is not persuasive and does not address the rejection as written above.

Applicant takes issue with the office action's rejection style that the rejection has not provided enough detail to address the long narrative claim language where single claims take up entire pages of text (page 32 of 49). The previous103 rejection was 8 pages of detailed text and the present rejection is nearly 16 pages of factual information detailing the preponderance of evidence in this crowded art in as clear and concise manner as possible. If the rejection is not clear then the Examiner refers Applicant to MPEP 707.07(d) paragraphs 2 and 3 for further clarification.

Applicant then presents claim 1 and asserts that several deficiencies are present. First, Applicant is incorrect in their interpretation of VasoKINOX treating a form of hypoxic respiratory failure or that none of the references teach 20 ppm of iNO is the recommended dose of iNO for the treatment of neonates. The Examiner has addressed this above.

Applicant then asserts that the second warning is required by the claim. The Examiner has stated clearly above that one can give any number of warnings of the well-known consequences of iNO administration, such as pulmonary edema, and it would remain obvious. The claimed subject matter as a whole is obvious.

Applicant asserts that belief in Kazeroonie is not warranted. This argument is not persuasive because Kazeroonie presents sound scientific fact while Applicant merely presents assumptions, speculation, possibilities and plausabilities. The preponderance

of evidence as a whole recognizes and understands that if you raise the PCWP to a certain level then pulmonary edema results.

Applicant disagrees about the motivation to combine the references because VasoKINOX is directed to cardiac surgery; the LVD of VasoKINOX does not apply to all LVD patients and there are no reasonable interpretations of the LVD contraindication in VasoKINOX that applies to the instantly claimed patient population. The Examiner has already soundly rejected all of these points previously and they are not persuasive for the reasons provided supra.

Applicant takes further stylistic issue with the rejection regarding missing limitations and motivations. However, the Examiner has addressed all the limitations of each and every claim as discussed above.

Applicant asserts that there is a “crucial misunderstanding” on the part of the Office and goes back again to the unsound argument of hypoxic respiratory failure argument. The Examiner again rejects this argument.

Applicant is confused as to why the Office Action mentions “performing echocardiography as this is not an element of any of the claims of this application,...". Perhaps Applicant should go back and read their own claims drawn to "determining" steps which require acquisition of information from the patient and the "performing at least one diagnostic process" step. The Examiner has properly cited echocardiography to determine LVD as required by the claims; the diagnostic process is not for determining hypoxic respiratory failure which is not required by the claims. The Examiner has met each and every claimed limitation in the body of the rejection above.

Applicant asserts that hypoxic respiratory failure is a distinctly different condition. This argument is moot since this repeated argument has been soundly addressed above.

Applicant strongly disagrees that there is reasonable expectation of success in producing the claimed invention. The Examine equally strongly disagrees but has the superior position with the preponderance of factual evidence supporting the Examiner's position. The Examiner has addressed the hypoxic respiratory failure in two different ways: one is implicit in the reference and the other is explicit in the newly cited art. Contrary to Applicant's opinion, the preponderance of art teaches and suggests a link between LVD in a neonate and risk of pulmonary edema upon treatment with iNO.

Next Applicant asserts that VasoKINOX disclosure is based on information known in the art as of April 05, 2007. The Report noted by Applicant is noted but not considered relevant as Applicant's reference has not been applied by the Examiner and one cannot look at the art in a vacuum. The Examiner must consider the art as a whole.

Applicant then discusses the INOT22 study and asserts that the risk of pulmonary edema in neonates was unexpected prior to the INOT22 study. The Examiner cannot agree because any treatment that raises the PCWP to a certain level above normal will cause pulmonary edema as explained in detail above and it is well known that iNO will increase PCWP. It is irrelevant if 100 medical professionals, IRBs and/or IECs did not find the claimed methods to be obvious. What the FDA requires as a label is not relevant. The Examiner is the fact finder not the 100 medical professionals, FDA, IRBs and/or IECs.

Applicant asserts that it is “a startling new finding, inconsistent with generally accepted assumptions in the art, that neonates with hypoxic respiratory failure and LVD are at risk of pulmonary edema when treated with inhaled nitric oxide." The Examiner cannot agree because it is well known in the art to administer iNO to neonates with pulmonary hypertension and/or hypoxic respiratory failure; iNO can cause an increase in PCWP and an increase in PCWP runs the risk of pulmonary edema. Case closed.

Response to Declarations filed under 37 CFR 1.132

Applicant filed declarations by Dr. Douglas Greene and James Baldassarre on 12/23/13.

The Baldassarre Declaration merely covers the INOT22 study and is an opinion declaration which is not probative of non-obviousness especially when Dr. Baldassarre has a high level of interest in the outcome of the case as he is the inventor. Furthermore, the strength of the preponderance of objective evidence for obviousness outweighs the opposing evidence of non-obviousness, which is just opinion based on the INOT22 study. The Examiner is the fact finder. MPEP 716.01(d) states: “Although the record may establish evidence of secondary considerations which are indicia of nonobviousness, the record may also establish such a strong case of obviousness that the objective evidence of nonobviousness is not sufficient to outweigh the evidence of obviousness.”

The Greene Declaration is the opinion of Dr. Greene of the arguments and interpretations presented by the USPTO. Dr. Greene states that pulmonary hypertension is not a form of hypoxic respiratory failure. However, each claim must be

given the broadest reasonable interpretation in light of the specification and Applicant teaches in [0002] that the two go hand in hand which is further supported by Dr. Greene in paragraph 9 of the Declaration when he states that the conditions coexist in the same patient. See the Examiner's full explanation *supra*. Additionally, the opinion Declaration is rendered moot since the newly cited art clearly teaches administration of iNO to neonates with hypoxic respiratory failure.

Summary:

The art already teaches and suggests providing generated compressed cylinders of nitric oxide gas to neonatal medical providers to treat neonatal patients who have pulmonary hypertension/hypoxic respiratory failure who are not dependent on right-to-left shunting of blood with 20 ppm of inhaled nitric oxide and performing diagnostic tests on patients to determine pre-existing LVD where an increase in PCWP can lead to pulmonary edema. Entangled in the claim language is a flow chart dependent on human intelligence alone to make mental decisions based on information already known in the art as discussed in great detail above. MPEP 2141 III states: "The proper analysis is whether the claimed invention would have been obvious to one of ordinary skill in the art after consideration of all the facts." After consideration of all the facts, Applicant's Declarations and arguments are not persuasive and the Examiner has reached a determination that the instant claims are not patentable in view of the preponderance of evidence which is more convincing than the evidence which has been offered in opposition to it.

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

Notice of References Cited	Application/Control No. 13/683,236	Applicant(s)/Patent Under Reexamination BALDASSARRE, JAMES S.	
	Examiner ERNST ARNOLD	Art Unit 1613	Page 1 of 2

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
	A	US-			
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	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	NEJM (NEJM 1997; 336(9):597-604)
	V	Smyth (Thorax 2000;55(suppl 1):S51-S55).
	W	Fromm et al. (The Journal of Emergency Medicine 1995, 13(1):71-87).
	X	Burkhoff et al. (Am J Physiol 1993, 34:H1819-H1828)

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
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	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	Bernasconi et al. (Images Paediatr Cardiol; 2002, 4(1):4-29).
	V	
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
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EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
S1	1	"20100330206".pn. and ((supply or supplying) and (medical adj provider) and responsible)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2013/04/12 14:50
S2	1	"20100330206".pn. and ((supply or supplying) and (medical adj provider) and responsible and (delivery with device))	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2013/04/12 14:51
S3	0	"20100330206".pn. and (source with ((compressed adj gas) or (delivery adj devicd)))	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2013/04/12 14:52
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S5	1	"20130078321".pn. and (source with ((compressed adj gas) or (delivery adj device)))	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2013/04/12 14:54
S6	1	"20100330206".pn. and ((compressed adj gas) or (delivery adj device))	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2013/04/12 14:57
S7	1	"20100331405".pn. and ((compressed adj gas) or (delivery adj device))	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2013/04/12 14:59
S8	0	"20130078321".pn. and (distribute or distributing)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2013/04/12 15:24
S9	0	"20100331405".pn. and (distribute or distributing)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2013/04/12 15:26
S10	0	"8431163".pn. and (distribute or distributing)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2013/04/12 15:28
S11	0	"20100330206".pn. and (distribute or distributing)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2013/04/12 15:29
S12	0	"13683236" and benefit and outweigh and potential	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2013/04/20 10:45

S13	1	"13683236" and (benefit with potential)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2013/04/20 10:45
S14	42	baldassarre.in. and (generate or generated or generating)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2014/02/03 09:14
S15	0	baldassarre.in. and ((generate or generated or generating) with cylinder)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2014/02/03 09:15
S16	1	baldassarre.in. and ((warn or warning) with (first or second))	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2014/02/03 09:28
S17	1	"12820866" and ((warn or warning) with (first or second))	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2014/02/03 09:31
S18	4	"12820866"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2014/02/03 09:31
S19	7	"12821041"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2014/02/03 11:39
S20	2	"12821041" and (warn or warning)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2014/02/03 11:40
S21	1	"13683236"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2014/02/03 15:09

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	Application Number	13683236
	Filing Date	2012-11-21
	First Named Inventor	Baldassarre
	Art Unit	1613
	Examiner Name	Ernst V. Arnold
	Attorney Docket Number	26047-0003006

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	Examiner Name	Ernst V. Arnold
	Attorney Docket Number	26047-0003006

	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	☐

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	Examiner Name	Ernst V. Arnold
	Attorney Docket Number	26047-0003006

	12	Hayward et al., Inhaled nitric oxide in cardiology practice; Cardiovascular Research 43:628-638 (1999)	☐
	13	Mourani, et al., Left Ventricular Diastolic Dysfunction in Bronchopulmonary Dysplasia; J. of Pediatrics; 152:291-293 (2008)	☐
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Examiner Signature	/Ernst Arnold/	Date Considered	01/31/2014

*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.

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	First Named Inventor	Baldassarre
	Art Unit	1613
	Examiner Name	Ernst V. Arnold
	Attorney Docket Number	26047-0003006

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)	2013-12-23
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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Receipt date: 12/23/2013

Privacy Act Statement

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

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

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.

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

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

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

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

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

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

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

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13683236	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

SEARCH NOTES		
Search Notes	Date	Examiner
consultation with QAS Majorie Moran on 101 issues and drafting of rejection	12/21/12	eva
consultation with TC1600 MMoran on 101 issues and claim rejections	4/19/13	eva
search update EAST all databases	4/22/13	eva
consult SPE BKwon and SPE JVollano on priority date	2/4/14	eva
search update	2/4/14	eva

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

UNITED STATES PATENT AND TRADEMARK OFFICE

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

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/683,236	11/21/2012	James S. Baldassarre	26047-0003006	5655

94169 7590 03/18/2014

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

EXAMINER	
ARNOLD, ERNST V	
ART UNIT	PAPER NUMBER
1613	
MAIL DATE	DELIVERY MODE
03/18/2014	PAPER

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

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

Applicant-Initiated Interview Summary	Application No.	Applicant(s)	
	13/683,236	BALDASSARRE, JAMES S.	
	Examiner	Art Unit	
	ERNST V. ARNOLD	1613	

All participants (applicant, applicant's representative, PTO personnel):

(1) *ERNST V. ARNOLD*. (3)_____.

(2) *Janice Fraser*. (4)_____.

Date of Interview: *11 March 2014*.

Type: ☒ Telephonic ☐ Video Conference
☐ Personal [copy given to: ☐ applicant ☐ applicant's representative]

Exhibit shown or demonstration conducted: ☐ Yes ☐ No.
If Yes, brief description: _____.

Issues Discussed ☐101 ☐112 ☐102 ☐103 ☐Others
(For each of the checked box(es) above, please describe below the issue and detailed description of the discussion)

Claim(s) discussed: _____.

Identification of prior art discussed: _____.

Substance of Interview
(For each issue discussed, provide a detailed description and indicate if agreement was reached. Some topics may include: identification or clarification of a reference or a portion thereof, claim interpretation, proposed amendments, arguments of any applied references etc...)

Applicant discussed the priority issues which if resolved would appear to remove the primary reference of VasoKinox as prior art. Applicant discussed that the "product" issue can be fixed by amendment. Applicant stated that the first warning was incorporated by reference from the label in 12494598 and the concept of the second warning is present but the word "warning" is not ipsis verbis present. The Examiner asked that in their reply if sections in the spec for support could be cited. The term "generating" was discussed and while Applicant thought that it was more of a new matter issue, Applicant and the Examiner sought a resolution and tentatively agreed that deletion of 'generating' and insertion of 'obtaining' would rectify the issues raised in the Office Action. While the term 'obtaining' is also not ipsis verbis present, the gas cyclinder is supplied and therefore must have been obtained. If all the priority issues are resolved then it appears that the primary reference in the 103 rejection will no longer be prior art. The Examiner could not comment on patentability until after claim amendment(s) and arguments were filed as well as further consultation with specialists in the Office..

Applicant recordation instructions: The formal written reply to the last Office action must include the substance of the interview. (See MPEP section 713.04). If a reply to the last Office action has already been filed, applicant is given a non-extendable period of the longer of one month or thirty days from this interview date, or the mailing date of this interview summary form, whichever is later, to file a statement of the substance of the interview

Examiner recordation instructions: Examiners must summarize the substance of any interview of record. A complete and proper recordation of the substance of an interview should include the items listed in MPEP 713.04 for complete and proper recordation including the identification of the general thrust of each argument or issue discussed, a general indication of any other pertinent matters discussed regarding patentability and the general results or outcome of the interview, to include an indication as to whether or not agreement was reached on the issues raised.

☐ Attachment

/ERNST V ARNOLD/ Primary Examiner, Art Unit 1613	

Summary of Record of Interview Requirements

Manual of Patent Examining Procedure (MPEP), Section 713.04, Substance of Interview Must be Made of Record
A complete written statement as to the substance of any face-to-face, video conference, or telephone interview with regard to an application must be made of record in the application whether or not an agreement with the examiner was reached at the interview.

Title 37 Code of Federal Regulations (CFR) § 1.133 Interviews
Paragraph (b)

In every instance where reconsideration is requested in view of an interview with an examiner, a complete written statement of the reasons presented at the interview as warranting favorable action must be filed by the applicant. An interview does not remove the necessity for reply to Office action as specified in §§ 1.111, 1.135. (35 U.S.C. 132)

37 CFR §1.2 Business to be transacted in writing.
All business with the Patent or Trademark Office should be transacted in writing. The personal attendance of applicants or their attorneys or agents at the Patent and Trademark Office is unnecessary. The action of the Patent and Trademark Office will be based exclusively on the written record in the Office. No attention will be paid to any alleged oral promise, stipulation, or understanding in relation to which there is disagreement or doubt.

The action of the Patent and Trademark Office cannot be based exclusively on the written record in the Office if that record is itself incomplete through the failure to record the substance of interviews.

It is the responsibility of the applicant or the attorney or agent to make the substance of an interview of record in the application file, unless the examiner indicates he or she will do so. It is the examiner's responsibility to see that such a record is made and to correct material inaccuracies which bear directly on the question of patentability.

Examiners must complete an Interview Summary Form for each interview held where a matter of substance has been discussed during the interview by checking the appropriate boxes and filling in the blanks. Discussions regarding only procedural matters, directed solely to restriction requirements for which interview recordation is otherwise provided for in Section 812.01 of the Manual of Patent Examining Procedure, or pointing out typographical errors or unreadable script in Office actions or the like, are excluded from the interview recordation procedures below. Where the substance of an interview is completely recorded in an Examiners Amendment, no separate Interview Summary Record is required.

The Interview Summary Form shall be given an appropriate Paper No., placed in the right hand portion of the file, and listed on the "Contents" section of the file wrapper. In a personal interview, a duplicate of the Form is given to the applicant (or attorney or agent) at the conclusion of the interview. In the case of a telephone or video-conference interview, the copy is mailed to the applicant's correspondence address either with or prior to the next official communication. If additional correspondence from the examiner is not likely before an allowance or if other circumstances dictate, the Form should be mailed promptly after the interview rather than with the next official communication.

The Form provides for recordation of the following information:
- Application Number (Series Code and Serial Number)
- Name of applicant
- Name of examiner
- Date of interview
- Type of interview (telephonic, video-conference, or personal)
- Name of participant(s) (applicant, attorney or agent, examiner, other PTO personnel, etc.)
- An indication whether or not an exhibit was shown or a demonstration conducted
- An identification of the specific prior art discussed
- An indication whether an agreement was reached and if so, a description of the general nature of the agreement (may be by attachment of a copy of amendments or claims agreed as being allowable). Note: Agreement as to allowability is tentative and does not restrict further action by the examiner to the contrary.
- The signature of the examiner who conducted the interview (if Form is not an attachment to a signed Office action)

It is desirable that the examiner orally remind the applicant of his or her obligation to record the substance of the interview of each case. It should be noted, however, that the Interview Summary Form will not normally be considered a complete and proper recordation of the interview unless it includes, or is supplemented by the applicant or the examiner to include, all of the applicable items required below concerning the substance of the interview.

A complete and proper recordation of the substance of any interview should include at least the following applicable items:
1) A brief description of the nature of any exhibit shown or any demonstration conducted,
2) an identification of the claims discussed,
3) an identification of the specific prior art discussed,
4) an identification of the principal proposed amendments of a substantive nature discussed, unless these are already described on the Interview Summary Form completed by the Examiner,
5) a brief identification of the general thrust of the principal arguments presented to the examiner,
   (The identification of arguments need not be lengthy or elaborate. A verbatim or highly detailed description of the arguments is not required. The identification of the arguments is sufficient if the general nature or thrust of the principal arguments made to the examiner can be understood in the context of the application file. Of course, the applicant may desire to emphasize and fully describe those arguments which he or she feels were or might be persuasive to the examiner.)
6) a general indication of any other pertinent matters discussed, and
7) if appropriate, the general results or outcome of the interview unless already described in the Interview Summary Form completed by the examiner.

Examiners are expected to carefully review the applicant's record of the substance of an interview. If the record is not complete and accurate, the examiner will give the applicant an extendable one month time period to correct the record.

Examiner to Check for Accuracy

If the claims are allowable for other reasons of record, the examiner should send a letter setting forth the examiner's version of the statement attributed to him or her. If the record is complete and accurate, the examiner should place the indication, "Interview Record OK" on the paper recording the substance of the interview along with the date and the examiner's initials.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	: James S. Baldassarre	Art Unit	: 1613
Serial No.	: 13/683,236	Examiner	: Ernst V. Arnold
Filed	: November 21, 2012	Conf. No.	: 5655
Title	: METHODS OF DISTRIBUTING A PHARMACEUTICAL PRODUCT COMPRISING NITRIC OXIDE GAS FOR INHALATION		

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

AMENDMENT IN REPLY TO ACTION OF FEBRUARY 5, 2014

This application has Track 1 status. Please enter the following amendment.

List of claims (replacing prior versions).

1. (Currently Amended) A method of providing ~~a pharmaceutical product~~ pharmaceutically acceptable nitric oxide gas, the method comprising:

~~generating~~obtaining a cylinder containing compressed nitric oxide gas ~~by a process comprising compressing nitric oxide and nitrogen gases under high pressure~~ in the form of a gaseous blend of nitric oxide and nitrogen;

supplying the cylinder containing compressed nitric oxide gas to a medical provider responsible for treating ~~a plurality of~~ neonates ~~with~~who have hypoxic respiratory failure, including some who do not have left ventricular dysfunction ~~and who are not dependent on right-to-left shunting of blood~~;

~~informing~~ providing to the medical provider (i) information that a recommended dose of inhaled nitric oxide gas for treatment of neonates with hypoxic respiratory failure is 20 ppm nitric oxide~~;~~

~~providing a first warning to the medical provider that inhaled nitric oxide is contraindicated in the treatment of neonates dependent on right-to-left shunting of blood; and~~

~~providing a second warning to the medical provider, distinct from the first warning,~~ and (ii) information that, in patients with pre-existing left ventricular dysfunction, inhaled nitric oxide may increase pulmonary capillary wedge pressure (PCWP), leading to pulmonary edema, the ~~second warning~~ information of (ii) being sufficient to cause a medical provider considering inhaled nitric oxide treatment for a plurality of neonatal patients who (a) are suffering from a condition for which inhaled nitric oxide is indicated, and (b) have pre-existing left ventricular dysfunction, to elect to avoid treating one or more of the plurality of patients with inhaled nitric oxide in order to avoid putting the one or more patients at risk of pulmonary edema.

2.-5. (Canceled)

6. (Currently Amended) The method of claim 1, wherein the ~~dose recommendation and the first and second warnings~~ information of (i) and the information of (ii) appear in prescribing

information supplied to the medical provider with the cylinder containing compressed nitric oxide gas.

7. (Currently Amended) The method of claim 1, further comprising:

performing at least one diagnostic process to identify a first ~~neonate~~neonatal patient who has hypoxic respiratory failure and is a candidate for 20 ppm inhaled nitric oxide treatment~~, wherein the first neonate patient is not dependent on right to left shunting of blood~~;

determining that the first ~~neonate~~neonatal patient has pre-existing left ventricular dysfunction;

evaluating the potential benefit of treating the first ~~neonate~~neonatal patient with 20 ppm inhaled nitric oxide vs. the potential risk ~~described in the second warning~~ that inhaled nitric oxide could cause an increase in PCWP leading to pulmonary edema in patients who have pre-existing left ventricular dysfunction, in order to arrive at a decision of whether or not to treat the first ~~neonate~~neonatal patient with inhaled nitric oxide;

identifying a second neonatal patient as having hypoxic respiratory failure~~, not being dependent on right to left shunting of blood,~~ and not having left ventricular dysfunction; and

treating the second neonatal patient with 20 ppm inhaled nitric oxide.

8. (Currently Amended) The method of claim 1, further comprising:

performing at least one diagnostic process to identify a plurality of ~~neonate~~neonatal patients who have hypoxic respiratory failure and are candidates for inhaled nitric oxide treatment~~, wherein the patients of the plurality are not dependent on right to left shunting of blood~~;

determining prior to treatment with inhaled nitric oxide whether or not each patient of the plurality has pre-existing left ventricular dysfunction;

determining that a first patient of the plurality does not have pre-existing left ventricular dysfunction;

treating the first patient with 20 ppm inhaled nitric oxide;

determining that other patients of the plurality do have pre-existing left ventricular dysfunction;~~ and~~

for each patient of the plurality determined to have pre-existing left ventricular dysfunction, evaluating on a case-by-case basis the potential benefit of treating the patient with 20 ppm inhaled nitric oxide vs. the potential risk ~~described in the second warning~~ that inhaled nitric oxide could cause an increase in PCWP, leading to pulmonary edema;

for at least one patient of the plurality determined to have pre-existing left ventricular dysfunction, determining that the potential benefit of the treatment outweighs the potential risk described in the second warning; and

treating the at least one patient with 20 ppm inhaled nitric oxide.

9. (Currently Amended) The method of claim 7, wherein the ~~dose recommendation and the first and second warnings~~ information of (i) and the information of (ii) appear in prescribing information supplied to the medical provider with the cylinder containing compressed nitric oxide gas.

10. (Currently Amended) The method of claim 8, wherein the ~~dose recommendation and the first and second warnings~~ information of (i) and the information of (ii) appear in prescribing information supplied to the medical provider with the cylinder containing compressed nitric oxide gas.

11.-20. (Canceled)

21. (Currently Amended) A method of providing ~~a pharmaceutical product~~ pharmaceutically acceptable nitric oxide gas, the method comprising:

~~generating~~obtaining a cylinder containing compressed nitric oxide gas ~~by a process comprising compressing nitric oxide and nitrogen gases under high pressure~~ in the form of a gaseous blend of nitric oxide and nitrogen;

supplying the cylinder containing compressed nitric oxide gas to a medical provider responsible for treating ~~a plurality of~~ neonates ~~with~~who have hypoxic respiratory failure, including some who do not have pre-existing left ventricular dysfunction ~~and who are not dependent on right-to-left shunting of blood~~; and

~~informing~~ providing to the medical provider (i) information that a recommended dose of inhaled nitric oxide gas for treatment of neonates with hypoxic respiratory failure is 20 ppm nitric oxide~~;~~

~~providing a first warning to the medical provider that inhaled nitric oxide is contraindicated in the treatment of neonates dependent on right-to-left shunting of blood; and~~

~~providing a second warning to the medical provider, distinct from the first warning~~, (ii) information that patients who have pre-existing left ventricular dysfunction and are treated with inhaled nitric oxide may experience pulmonary edema, and ~~recommending~~ (iii) a recommendation that, if pulmonary edema occurs in a patient who has pre-existing left ventricular dysfunction and is treated with inhaled nitric oxide, the treatment with inhaled nitric oxide should be discontinued.

22.-24. (Canceled)

25. (Currently Amended) The method of claim 21, wherein the ~~dose recommendation and the first and second warnings~~ information of (i) and (ii) and the recommendation of (iii) appear in prescribing information supplied to the medical provider with the cylinder containing compressed nitric oxide gas.

26. (Currently Amended) The method of claim 21, further comprising:

performing at least one diagnostic process to identify a neonatal patient who has hypoxic respiratory failure and is a candidate for inhaled nitric oxide treatment;

determining prior to treatment with inhaled nitric oxide that the neonatal patient ~~is not dependent on right to left shunting of blood, but does have~~ has pre-existing left ventricular dysfunction ~~consistent with a pulmonary capillary wedge pressure greater than or equal to 20 mm Hg~~;

treating the neonatal patient with 20 ppm inhaled nitric oxide, whereupon the neonatal patient experiences pulmonary edema; and

~~following~~in accordance with the recommendation ~~in the second warning~~ of (iii), discontinuing the treatment with inhaled nitric oxide due to the neonatal patient's pulmonary edema.

27.-30. (Canceled)

31. (Previously presented) The method of claim 8, wherein the at least one patient is monitored for evidence of increased PCWP and/or for evidence of pulmonary edema during treatment with 20 ppm inhaled nitric oxide.

32. (Previously Presented) The method of claim 26, wherein the neonatal patient is monitored for evidence of increased PCWP and/or for evidence of pulmonary edema during treatment with 20 ppm inhaled nitric oxide.

33. (Currently Amended) A method ~~of providing a pharmaceutical product, the method~~ comprising:

obtaining a source of nitric oxide gas comprising a cylinder of compressed gas and/or a device that delivers nitric oxide gas into an inspiratory limb of a breathing circuit, for inhalation by a patient;

supplying [[a]]the source of nitric oxide gas to a medical provider responsible for treating ~~a plurality of~~ neonates ~~with~~who have hypoxic respiratory failure, including some who do not have left ventricular dysfunction ~~and who are not dependent on right-to-left shunting of blood, wherein the source comprises a cylinder of compressed gas and/or a delivery device suitable to deliver nitric oxide gas for inhalation by a patient~~; and

~~informing~~ providing to the medical provider (i) information that a recommended dose of inhaled nitric oxide gas for treatment of neonates with hypoxic respiratory failure is 20 ppm nitric oxide~~;~~

~~providing a first warning to the medical provider that inhaled nitric oxide is contraindicated in the treatment of neonates dependent on right-to-left shunting of blood; and~~

~~providing a second warning to the medical provider, distinct from the first warning,~~ and (ii) information that, in patients with pre-existing left ventricular dysfunction, inhaled nitric

oxide may increase PCWP, leading to pulmonary edema, the ~~second warning~~ information of (ii) being sufficient to cause a medical provider considering inhaled nitric oxide treatment for a plurality of neonatal patients who (a) are suffering from a condition for which inhaled nitric oxide is indicated, and (b) have pre-existing left ventricular dysfunction, to elect to avoid treating one or more of the plurality of patients with inhaled nitric oxide in order to avoid putting the one or more patients at risk of pulmonary edema~~;~~

~~performing at least one diagnostic process to identify a first neonate patient who has hypoxic respiratory failure and is a candidate for 20 ppm inhaled nitric oxide treatment, wherein the first neonate patient is not dependent on right to left shunting of blood;~~

~~determining that the first neonate patient has pre-existing left ventricular dysfunction;~~

~~evaluating the potential benefit of treating the first neonate patient with 20 ppm inhaled nitric oxide vs. the potential risk described in the second warning that inhaled nitric oxide could cause an increase in PCWP leading to pulmonary edema in patients who have pre-existing left ventricular dysfunction, in order to arrive at a decision of whether or not to treat the first neonate patient with inhaled nitric oxide;~~

~~identifying a second neonatal patient as having hypoxic respiratory failure, not being dependent on right to left shunting of blood, and not having left ventricular dysfunction; and~~

~~treating the second neonatal patient with 20 ppm inhaled nitric oxide~~.

34. (Currently Amended) The method of claim 33, wherein the ~~dose recommendation and the first and second warnings~~ information of (i) and the information of (ii) appear in prescribing information supplied to the medical provider with the source of nitric oxide gas.

35. (Currently Amended) A method ~~of providing a pharmaceutical product, the method~~ comprising:

obtaining a device that delivers nitric oxide gas into an inspiratory limb of a breathing circuit, for inhalation by a patient;

supplying ~~a source of nitric oxide gas~~the device to a medical provider responsible for treating ~~a plurality of~~ neonates ~~with~~who have hypoxic respiratory failure, including some who do not have pre-existing left ventricular dysfunction ~~and who are not dependent on right-to-left~~

~~shunting of blood, wherein the source comprises a cylinder of compressed gas and/or a delivery device suitable to deliver nitric oxide gas for inhalation by a patient~~;

~~informing~~providing to the medical provider (i) information that a recommended dose of inhaled nitric oxide gas for treatment of neonates with hypoxic respiratory failure is 20 ppm nitric oxide~~;~~

~~providing a first warning to the medical provider that inhaled nitric oxide is contraindicated in the treatment of neonates dependent on right-to-left shunting of blood; and~~

~~providing a second warning to the medical provider, distinct from the first warning,~~ and (ii) information that, in patients with pre-existing left ventricular dysfunction, inhaled nitric oxide may increase PCWP, leading to pulmonary edema, the ~~second warning~~ information of (ii) being sufficient to cause a medical provider considering inhaled nitric oxide treatment for ~~a plurality of~~ multiple neonatal patients who (a) are suffering from ~~a condition for which inhaled nitric oxide is indicated~~hypoxic respiratory failure, and (b) have pre-existing left ventricular dysfunction, to elect to avoid treating one or more of the ~~plurality of~~multiple patients with inhaled nitric oxide in order to avoid putting the one or more patients at risk of pulmonary edema~~;~~

~~performing at least one diagnostic process to identify a plurality of neonate patients who have hypoxic respiratory failure and are candidates for inhaled nitric oxide treatment, wherein the patients of the plurality are not dependent on right to left shunting of blood;~~

~~determining prior to treatment with inhaled nitric oxide whether or not each patient of the plurality has pre-existing left ventricular dysfunction;~~

~~determining that a first patient of the plurality does not have pre-existing left ventricular dysfunction;~~

~~treating the first patient with 20 ppm inhaled nitric oxide;~~

~~determining that other patients of the plurality do have pre-existing left ventricular dysfunction; and~~

~~for each patient of the plurality determined to have pre-existing left ventricular dysfunction, evaluating on a case-by-case basis the potential benefit of treating the patient with 20 ppm inhaled nitric oxide vs. the potential risk described in the second warning that inhaled nitric oxide could cause an increase in PCWP, leading to pulmonary edema;~~

~~for at least one patient of the plurality determined to have pre-existing left ventricular dysfunction, determining that the potential benefit of the treatment outweighs the potential risk described in the second warning; and~~

~~treating the at least one patient with 20 ppm inhaled nitric oxide~~.

36. (Currently Amended) The method of claim [[1]] 35, wherein the ~~dose recommendation and the first and second warnings~~ information of (i) and the information of (ii) appear in prescribing information supplied to the medical provider with the ~~source of nitric oxide gas~~ device.

37. (New) The method of claim 33, further comprising:

identifying a first neonatal patient who has hypoxic respiratory failure and is a candidate for 20 ppm inhaled nitric oxide treatment;

determining that the first neonatal patient has pre-existing left ventricular dysfunction;

evaluating the potential benefit of treating the first neonatal patient with 20 ppm inhaled nitric oxide vs. the potential risk described in the information of (ii) that inhaled nitric oxide could cause an increase in PCWP leading to pulmonary edema in patients who have pre-existing left ventricular dysfunction, in order to arrive at a decision of whether or not to treat the first neonatal patient with inhaled nitric oxide;

identifying a second neonatal patient as having hypoxic respiratory failure and not having left ventricular dysfunction; and

using the source of nitric oxide gas to treat the second neonatal patient with 20 ppm inhaled nitric oxide.

38. (New) The method of claim 33, further comprising:

identifying a plurality of neonatal hypoxic respiratory failure patients who are candidates for inhaled nitric oxide treatment;

determining prior to treatment with inhaled nitric oxide whether or not each patient of the plurality has pre-existing left ventricular dysfunction, thereby determining that a first patient of the plurality does not have pre-existing left ventricular dysfunction;

using the source of nitric oxide gas to treat the first patient with 20 ppm inhaled nitric oxide;

determining that other patients of the plurality do have pre-existing left ventricular dysfunction;

for each patient of the plurality who is determined to have pre-existing left ventricular dysfunction, evaluating on a case-by-case basis the potential benefit of treating the patient with 20 ppm inhaled nitric oxide vs. the potential risk described in the information of (ii) that inhaled nitric oxide could cause an increase in PCWP, leading to pulmonary edema;

for at least one of the evaluated patients, determining that the potential benefit of the treatment outweighs the potential risk; and

using the source of nitric oxide gas to treat the at least one patient with 20 ppm inhaled nitric oxide.

39. (New) The method of claim 35, further comprising:

identifying a first neonatal patient who has hypoxic respiratory failure and is a candidate for 20 ppm inhaled nitric oxide treatment;

determining that the first neonatal patient has pre-existing left ventricular dysfunction;

evaluating the potential benefit of treating the first neonatal patient with 20 ppm inhaled nitric oxide vs. the potential risk described in the information of (ii) that inhaled nitric oxide could cause an increase in PCWP leading to pulmonary edema in patients who have pre-existing left ventricular dysfunction, in order to arrive at a decision of whether or not to treat the first neonatal patient with inhaled nitric oxide;

identifying a second neonatal patient as having hypoxic respiratory failure and not having left ventricular dysfunction; and

using the device to treat the second neonatal patient with 20 ppm inhaled nitric oxide.

40. (New) The method of claim 35, further comprising:

identifying a plurality of neonatal hypoxic respiratory failure patients who are candidates for inhaled nitric oxide treatment;

determining, prior to treatment with inhaled nitric oxide, whether or not each patient of the plurality has pre-existing left ventricular dysfunction, thereby determining that a first patient of the plurality does not have pre-existing left ventricular dysfunction;

using the device to treat the first patient with 20 ppm inhaled nitric oxide;

determining that other patients of the plurality do have pre-existing left ventricular dysfunction;

for each patient of the plurality who is determined to have pre-existing left ventricular dysfunction, evaluating on a case-by-case basis the potential benefit of treating the patient with 20 ppm inhaled nitric oxide vs. the potential risk described in the information of (ii) that inhaled nitric oxide could cause an increase in PCWP, leading to pulmonary edema;

for at least one of the evaluated patients, determining that the potential benefit of the treatment outweighs the potential risk; and

using the device to treat the at least one patient with 20 ppm inhaled nitric oxide.

REMARKS

Upon entry of the above amendment, claims 1, 6-10, 21, 25, 26, and 31-40 will be pending, new claims 37-40 having been added. Claims 2-5, 11-20, 22-24, and 27-30 were previously canceled. Claims 1, 6-10, 21, 25, 26, and 33-36 are presently amended. The amendments to independent claims 1 and 21 are supported in the specification at, for example, paragraphs [0005], [0020], and [0021]. The amendments to independent claims 33 and 35 are supported at, for example, paragraphs [0020] - [0022]. Dependent claims 6-10, 25, 26, 34, and 36 are amended to be consistent with the claims from which they depend; the dependency of claim 36 is also corrected (from claim 1 to claim 35). New claims 37 and 39 depend from claims 33 and 35, respectively, and specify some of the limitations previously in claim 33, as well as in claim 7. New claims 38 and 40 depend from claims 33 and 35, respectively; these new claims specify some of the limitations previously in claim 35, as well as in claim 8.

The total number of claims remains under the 30-claim limit required for Track 1 status. All pending claims are under examination.

Substance of the March 11, 2014 Interview

Applicant thanks Examiner Arnold for the courtesy of a telephonic interview with the undersigned on March 11, 2014, during which the priority issues raised in the Office Action dated February 5, 2014, were discussed (the "Interview"). Examiner Arnold provided helpful advice regarding the basis for the priority issues and possible claim amendments that, as applicant understands it, would likely overcome the priority issues without raising new issues under 35 USC § 101. Applicant is very grateful for the advice and has closely implemented it in this Reply. As acknowledged by Examiner Arnold during the Interview, if the priority issues are resolved so that it is clear the claims are entitled to their 2009 priority date, the VasoKINOX reference will be citable only under 35 USC § 102(a) and so can be removed by appropriate evidence of earlier invention (such as the evidence already of record). The Examiner also noted that, if the VasoKINOX reference is removed as prior art, the present obviousness rejection "implodes."

The priority issues and the Examiner's advice are described in detail below.

Priority

The present Office Action at pages 3-4 raises three concerns regarding claim language that, according to the Office Action, is not disclosed in the applications to which the present application claims priority. According to the Office Action, this means that the claims are not entitled to claim priority to a date earlier than the present application's filing date, i.e., November 21, 2012. While applicant maintains that the priority applications contained disclosure sufficient to support all of the claims even prior to the present amendments, the claims are newly amended consistent with the Examiner's advice during the Interview, in an effort to resolve the issues and thereby secure rapid allowance.

The first of the priority concerns centers on the phrase "providing a pharmaceutical product" in the preamble of each of the independent claims (claims 1, 21, 33, and 35). The Office Action states that "[the] priority documents disclose methods of 'providing pharmaceutically acceptable nitric oxide gas'…but do not disclose providing any pharmaceutical product but only nitric oxide gas." To address this issue, the present amendment deletes the phrase "providing a pharmaceutical product" from each of the independent claims. The preambles of independent claims 1 and 21 now recite, "**A method of providing pharmaceutically acceptable nitric oxide gas, the method comprising:**"; this employs an alternate phrase that the Office Action acknowledges is disclosed in the priority documents. The preambles of claims 33 and 35 are handled somewhat differently. The methods claimed in independent claims 33 and 35 encompass provision of a device that delivers nitric oxide gas (claim 35), or provision of a source of nitric oxide gas (claim 33), the source being a cylinder of gas and/or a device that delivers nitric oxide gas. Thus, the preambles of these two claims 33 and 35 now say simply, "**A method comprising:**". Since there is no question that the specification discloses "methods," applicant believes that these amendments to the preambles should resolve the Examiner's concern regarding the preamble language raised in the Office Action.

The second concern regarding claim language focuses on the step of "generating a cylinder containing compressed nitric oxide gas…" that was added to claims 1 and 21 in the

amendment filed December 23, 2013.[1] During the Interview, the Examiner helpfully suggested that this step be rewritten as "obtaining a cylinder…," a phrasing the Examiner noted is implicitly supported by the discussion of supplying a cylinder of NO gas in paragraph [0021] of the specification. Applicant has followed the Examiner's suggestion, replacing the "generating" step in both claims 1 and 21 with the following language: "**obtaining a cylinder containing compressed nitric oxide gas in the form of a gaseous blend of nitric oxide and nitrogen**." The Examiner acknowledged during the Interview that the claims so amended (which then would specify both "obtaining" and "supplying" the cylinder) would be considered to have an "active step" sufficient to satisfy 35 USC § 101. Thus, it is believed that the present amendment resolves the new matter/priority concern without raising any new issues.

The third concern regarding claim language derives from the "first warning" and "second warning" specified in each of the independent claims. Based on the discussion in the Interview, applicant understands the Examiner to be concerned that (a) the word "warning" does not appear in the priority applications, and (b) the priority applications allegedly do not explicitly disclose that *both* warnings should be communicated to a medical provider. In addition, the Examiner asked that applicant point out support in the priority applications for the elements of the "second warning" as recited in the claims.

To address part (a) of the Examiner's third concern, applicant has amended the claims so they no longer include the word "warning." Although the *substance* of what was previously labeled in the claims as a "first warning" and a "second warning" is certainly described in the specification of the each of the priority applications,[2] and is fairly characterized as "warnings," the present amendment moots the issue by entirely omitting reference to what had been the "first warning" and by referring to what previously had been labeled the "second warning" as "information." The word "information" is consistent with the term "informing" that appears in

[1] Applicant notes for the record that, since the challenged "generating a cylinder" language was added during prosecution and was not in the claims as originally filed with the application, the Office's objection to it is more accurately characterized as a "new matter" written description issue than as a priority issue.

[2] The content of the "first warning" regarding the contraindication for patients dependent on right-to-left shunting of blood is in the INOmax® inhaled nitric oxide prescribing information that was incorporated by reference in the priority applications. See, e.g., paragraph [0021] of the earliest priority application, U.S. Application Serial No. 12/494,598, filed June 30, 2009. Support for the content of the "second warning" is described in detail beginning at page 15 of the present Reply.

the priority applications in conjunction with disclosure of how the description of the risk of adverse events associated with left ventricular dysfunction is communicated to the medical provider. See, e.g., U.S. Application Serial No. 12/494,598, filed June 30, 2009 (the "'598 application"), at paragraphs [0006] and [0007].

Regarding part (b) of the Examiner's third concern: the claims no longer mention the first warning (i.e., that inhaled nitric oxide is contraindicated in the treatment of neonates who are dependent on right-to-left shunting of blood). Although the priority applications incorporated by reference the then-existing INOmax® inhaled nitric oxide prescribing information, so are deemed to have disclosed this contraindication from the prescribing information as being information that would have been provided to a medical provider (i.e., consistent with how it was presented in the claims prior to the present amendment), the present amendment moots this issue by entirely removing reference to this contraindication from the claims.

Finally, as noted above, the Examiner requested during the Interview that applicant describe in this response where support can be found in the priority applications for the details of the "second warning" as specified in the claims. This was just a general request; no particular deficit or area of concern was identified by the Examiner. Applicant is happy to oblige.

The relevant passage of claim 1, as presently amended, reads as follows:

> (ii) information that, in patients with pre-existing left ventricular dysfunction, inhaled nitric oxide may increase pulmonary capillary wedge pressure (PCWP), leading to pulmonary edema, the information of (ii) being sufficient to cause a medical provider considering inhaled nitric oxide treatment for a plurality of neonatal patients who (a) are suffering from a condition for which inhaled nitric oxide is indicated, and (b) have pre-existing left ventricular dysfunction, to elect to avoid treating one or more of the plurality of patients with inhaled nitric oxide in order to avoid putting the one or more patients at risk of pulmonary edema.

Detailed support for that passage is described below.

- The concept of "**in patients with pre-existing left ventricular dysfunction, inhaled nitric oxide may increase pulmonary capillary wedge pressure (PCWP), leading to pulmonary edema**" is supported in the '598 application at, for example, original claim 8 (combined with

original claim 1, from which it depends) and original claim 19 (combined with original claim 16, from which it depends), and in paragraphs [0005], [0018], [0052], and [0069].

- The concept of "**a medical provider considering inhaled nitric oxide treatment for a plurality of neonatal patients who are suffering from a condition for which inhaled nitric oxide is indicated**" is supported in the '598 application, for example, in the title and in paragraphs [0005]-[0009], [0019], [0021], [0034]-[0037], and [0039]-[0043].

- The concept that information about the risk of pulmonary edema is provided to the medical provider is supported in the '598 application at, for example, original claims 16, 19, 20, 22, and 23, and in paragraphs [0005]-[0007] and [0010]-[0011].

- The concept that the information about the risk would be "**sufficient to cause a medical provider…to elect to avoid treating one or more of the plurality of patients with inhaled nitric oxide in order to avoid putting the one or more patients at risk**" is supported in the '598 application at, for example, original claims 1, 8, 9, 24, and 25, and in paragraphs [0005], [0008], and [0009].

It is believed that the above description of the disclosure in the priority application thoroughly addresses the question posed by the Examiner in the Interview regarding where support for the details of the "second warning" (now referred to in claim 1 as "the information of (ii)") can be found in the priority application. If the Examiner would like further details regarding support for this or any other element of claim 1 (or of any other claim) in the '598 application, he is invited to telephone the undersigned to request those details be submitted.

All of the priority issues raised in the Office action and the Interview having now been resolved, applicant submits that the claims as currently amended are fully entitled to the June 30, 2009, filing date of the '598 application. Acknowledgement of that fact is respectfully requested.

Rejections under 35 USC § 103(a)

The Office action rejected all of the pending claims (i.e., claims 1, 6-10, 21, 25, 26, and 31-36) as obvious over a combination of references of which the VasoKINOX prescribing information is the primary reference. VasoKINOX bears a date of July 14, 2008, which is less than a year before the present application's June 30, 2009, priority date. Since the present claims are fully supported by written description in the June 30, 2009 priority application, it follows that VasoKINOX does not qualify as prior art under 35 USC § 102(b). In the Reply filed December 23, 2013, applicant submitted evidence including a Declaration under 37 C.F.R. § 1.131 establishing that VasoKINOX also does not qualify as prior art under 35 USC § 102(a). The Examiner agreed during the Interview that, once all of the priority issues were resolved (as has been done above), the primary reference will no longer be prior art against the claims and the obviousness rejections as presented in the Office action will "implode." It therefore appears to be unnecessary for applicant to address the merits of the Office action's obviousness arguments based on VasoKINOX (in combination with other references) at this time, other than to say that applicant disagrees with them at least for reasons of record and is prepared to elaborate if necessary. Withdrawal of the obviousness rejection based upon the present record is respectfully requested.

It is believed that all issues raised in the Office action have been addressed and all claims currently presented are allowable. If any issues remain, the Examiner is asked to telephone the undersigned so they can be quickly resolved to move the case to allowance.

Apply any necessary charges or credits to Deposit Account 06-1050, referencing the above attorney docket number.

Respectfully submitted,

Date: May 1, 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

23160889.doc

Electronic Acknowledgement Receipt	
EFS ID:	18917576
Application Number:	13683236
International Application Number:	
Confirmation Number:	5655
Title of Invention:	METHODS OF DISTRIBUTING A PHARMACEUTICAL PRODUCT COMPRISING NITRIC OXIDE GAS FOR INHALATION
First Named Inventor/Applicant Name:	James S. Baldassarre
Customer Number:	94169
Filer:	Janis K. Fraser/Mary Zynda
Filer Authorized By:	Janis K. Fraser
Attorney Docket Number:	26047-0003006
Receipt Date:	01-MAY-2014
Filing Date:	21-NOV-2012
Time Stamp:	14:41:05
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		26047_0003006_Resp.PDF	227808 b090d2fda3f10a55bc107acc00e6b504f7d7e80e	yes	17

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Amendment/Req. Reconsideration-After Non-Final Reject	1	1
	Claims	2	11
	Applicant Arguments/Remarks Made in an Amendment	12	17
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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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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99)**		
	Application Number	13683236
	Filing Date	2012-11-21
	First Named Inventor	Baldassarre
	Art Unit	1613
	Examiner Name	
	Attorney Docket Number	26047-0003006

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	13683236
	Filing Date	2012-11-21
	First Named Inventor	Baldassarre
	Art Unit	1613
	Examiner Name	
	Attorney Docket Number	26047-0003006

	1	PRAXAIR, INC. Protest filed against CA2,671,029 on June 2, 2014 (38 pages)	☐
	2	Prior art notice issued in CA267102 on August 9, 2013 (51 pages)	☐
	3	Stewart et al.; Hypoxic Respiratory Failure: Diagnosis and Treatment, 36th Annual Pacific Northwest Regional Respiratory Care Conference and Scientific Assembly; Apr. 26, 2009; pp. 1-71	☐

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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	13683236
	Filing Date	2012-11-21
	First Named Inventor	Baldassarre
	Art Unit	1613
	Examiner Name	
	Attorney Docket Number	26047-0003006

CERTIFICATION STATEMENT

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

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

OR

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

☐ See attached certification statement.

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

☐ A certification statement is not submitted herewith.

SIGNATURE

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

Signature	/Janis K. Fraser/	Date (YYYY-MM-DD)	2014-06-25
Name/Print	Janis K. Fraser	Registration Number	34819

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

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

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Electronic Patent Application Fee Transmittal	
Application Number:	13683236
Filing Date:	21-Nov-2012
Title of Invention:	METHODS OF DISTRIBUTING A PHARMACEUTICAL PRODUCT COMPRISING NITRIC OXIDE GAS FOR INHALATION
First Named Inventor/Applicant Name:	James S. Baldassarre
Filer:	Janis K. Fraser/Christine Grace
Attorney Docket Number:	26047-0003006
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:	19410599
Application Number:	13683236
International Application Number:	
Confirmation Number:	5655
Title of Invention:	METHODS OF DISTRIBUTING A PHARMACEUTICAL PRODUCT COMPRISING NITRIC OXIDE GAS FOR INHALATION
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:	26047-0003006
Receipt Date:	25-JUN-2014
Filing Date:	21-NOV-2012
Time Stamp:	16:08:11
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	2553
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Authorized User	

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)	IDS.pdf	612017 8c30f537a552353f430f5e33f8b174905b6417b8	no	4
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4	Non Patent Literature	prior.pdf	2620530 4fb792c0ac5f04d1856c80c2b53a4194b9bea1b0	no	51
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5	Fee Worksheet (SB06)	fee-info.pdf	30465 940652862a1c0960a7663dcd8284a70dd62934e7	no	2
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New International Application Filed with the USPTO as a Receiving Office
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/683,236	11/21/2012	James S. Baldassarre	26047-0003006	5655

94169 7590 07/16/2014
Fish & Richardson PC
P.O.Box 1022
minneapolis, MN 55440

EXAMINER	
ARNOLD, ERNST V	
ART UNIT	PAPER NUMBER
1613	
MAIL DATE	DELIVERY MODE
07/16/2014	PAPER

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

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

Office Action Summary	Application No. 13/683,236	Applicant(s) BALDASSARRE, JAMES S.	
	Examiner ERNST V. ARNOLD	Art Unit 1613	AIA (First Inventor to File) Status No

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

Period for Reply

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

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

Status

1)☒ Responsive to communication(s) filed on 5/1/14.

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

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

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

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

Disposition of Claims*

5)☒ Claim(s) 1,6-10,21,25,26 and 31-40 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) 1,6-10,21,25,26 and 31-40 is/are rejected.

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

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

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

Application Papers

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

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

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

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

Priority under 35 U.S.C. § 119

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

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

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

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

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

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

Attachment(s)

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

2) ☒ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date 6/25/14.

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

4) ☐ Other: _____.

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

DETAILED ACTION

Claims 2-5, 11-20, 22-24 and 27-30 have been cancelled. Claims 37-40 are new. Claims 1, 6-10, 21, 25, 26 and 31-40 are pending. Applicant's amendment necessitated a new ground of rejection. Accordingly, this Action is FINAL.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on 6/25/14 was filed after the mailing date of the Office Action on 2/5/14. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Withdrawn rejections:

Applicant's amendments and arguments filed 5/1/14 are acknowledged and have been fully considered. The Examiner has re-weighed all the evidence of record. Any rejection and/or objection not specifically addressed below is herein withdrawn.

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

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory double patenting rejection is appropriate where the claims at issue are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

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

The USPTO internet Web site contains terminal disclaimer forms which may be used. Please visit http://www.uspto.gov/forms/. The filing date of the application will determine what form should be used. A web-based eTerminal Disclaimer may be filled

out completely online using web-screens. An eTerminal Disclaimer that meets all requirements is auto-processed and approved immediately upon submission. For more information about eTerminal Disclaimers, refer to http://www.uspto.gov/patents/process/file/efs/guidance/eTD-info-I.jsp.

Claims 1, 6-10, 21, 25, 26 and 31-40 are rejected on the ground of nonstatutory double patenting as being unpatentable over:

1. Claims 1-25 of U.S. Patent No. 8431163 drawn to, for example: 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.

2. Claims 1-30 of U.S. Patent No. 8293284 drawn to, for example: A method of treatment comprising: (a) identifying a plurality of term or near-term neonate patients who are in need of 20 ppm inhaled nitric oxide treatment, wherein the patients are not dependent on right-to-left shunting of blood; (b) in a first patient of the plurality,

measuring pulmonary capillary wedge pressure to determine that the 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) in a second patient of the plurality, performing echocardiography and/or measurement of pulmonary capillary wedge pressure to determine that the 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.

3. Claims 1-30 of U.S. Patent No. 8282966 drawn to, for example: 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.

4. Claims 1-44 of 13683417 (Notice of Allowance filed 6/23/14 but not yet issued) drawn to, for example:

> 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.

Although the claims at issue are not identical, they are not patentably distinct from each other because the instant claims have been amended to providing pharmaceutically acceptable nitric oxide gas by obtaining a cylinder containing nitric oxide gas. This is implicit in the issued and issuing patents otherwise one could not administer 20 ppm inhaled NO treatment to the patient as the gas must be routed from the cylinder to some limb of a breathing circuit device for the patient to inhale. Consequently, the ordinary artisan would have recognized the obvious variation of the instantly claimed subject matter over the patented subject matter.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

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

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

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

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

/ERNST V ARNOLD/
Primary Examiner, Art Unit 1613

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13683236	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

SEARCH NOTES		
Search Notes	Date	Examiner
consultation with QAS Majorie Moran on 101 issues and drafting of rejection	12/21/12	eva
consultation with TC1600 MMoran on 101 issues and claim rejections	4/19/13	eva
search update EAST all databases	4/22/13	eva
consult SPE BKwon and SPE JVollano on priority date	2/4/14	eva
search update	2/4/14	eva
updated IDS	7/11/14	eva

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

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	13683236
Filing Date	2012-11-21
First Named Inventor	Baldassarre
Art Unit	1613
Examiner Name	
Attorney Docket Number	26047-0003006

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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	1							☐

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

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

Receipt date: 06/25/2014	Application Number	13683236	13683236 - 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		
	Attorney Docket Number	26047-0003006	

/E.A./	1	PRAXAIR, INC. Protest filed against CA2,671,029 on June 2, 2014 (38 pages)	☐
/E.A./	2	Prior art notice issued in CA267102 on August 9, 2013 (51 pages)	☐
/E.A./	3	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	☐

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	07/11/2014

*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.

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

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Named Inventor	:	James S. Baldassarre	Art Unit	:	1613
Serial No.	:	13/683,236	Examiner	:	Ernst V. Arnold
Filed	:	November 21, 2012	Conf. No.	:	5655
Title	:	METHODS OF DISTRIBUTING A PHARMACEUTICAL PRODUCT COMPRISING NITRIC OXIDE GAS FOR INHALATION			

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

REPLY TO FINAL ACTION OF JULY 16, 2014

In response to the Final Action, please consider the following remarks.

REMARKS

Claims 1, 6-10, 21, 25, 26 and 31-40 remain pending in the case, claims 2-5, 11-20, 22-24, and 27-30 having been previously canceled. No new amendments are presently proposed.

Applicants note with gratitude that all prior rejections have been withdrawn by the Office.

The present Office action imposes a single new ground of rejection: for obviousness-type double patenting over the claims of each of three patents (U.S. Patent Nos. 8,431,163; 8,293,284; and 8,282,966) and allowed application serial no. 13/683,417. Applicants note that the present claims are part of a restriction group separate from the restriction group pursued in the three patents and allowed application, and accordingly the present application was filed as a divisional. That means that the provisions of 35 U.S.C. § 121 apply to protect the present claims from rejection for obviousness-type double patenting over the other cases. Thus, no terminal disclaimer should be required in the present case. Nevertheless, in order to obviate the rejection and move the present claims efficiently toward allowance, applicants submit a terminal disclaimer and the associated fee with this reply. Apply that fee and any other necessary charges or credits to Deposit Account 06-1050, referencing the above attorney docket number.

Respectfully submitted,

Date: July 21, 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

23262594.doc

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Named Inventor	:	James S. Baldassarre	Art Unit	:	1613
Serial No.	:	13/683,236	Examiner	:	Ernst V. Arnold
Filed	:	November 21, 2012	Conf. No.	:	5655
Title	:	METHODS OF DISTRIBUTING A PHARMACEUTICAL PRODUCT COMPRISING NITRIC OXIDE GAS FOR INHALATION			

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[1] to Ikaria Holdings, Inc. The document was recorded in the Patent and Trademark Office at Reel 029352, Frame 0788.

2. From Ikaria Holdings, Inc. to Ikaria, Inc. The document was recorded in the Patent and Trademark Office at Reel 029353, Frame 0067.

3. From Ikaria, Inc. to INO Therapeutics LLC. The document was recorded in the Patent and Trademark Office at Reel 029353, Frame 0573, and again at Reel 032387, Frame 0802.

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

[1] Inventorship was later corrected to omit Ralf Rosskamp as a co-inventor, leaving James S. Baldassarre as the sole inventor. See change of inventorship papers filed on November 19, 2013.

date of the full statutory term of any patent listed in the attached Exhibit A, or of any U.S. patent that issues from the patent application listed in Exhibit A (together, these four patents are the "Exhibit A Patents"). The assignee hereby agrees that any patent granted on the instant application shall be enforceable only for and during such period that it is commonly owned with each of the Exhibit A Patents and the patent application listed in Exhibit A.

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

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

The fees totaling $640 for four terminal disclaimers, as required by 37 C.F.R. § 1.20(d), are being paid on the Electronic Filing System. Apply those fees and any other necessary charges or credits to Deposit Account 06-1050, referencing the above attorney docket number.

Respectfully submitted,

Date: July 21, 2014

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

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

23262675.doc

EXHIBIT A

1. U.S. Patent No. 8,431,163
2. U.S. Patent No. 8,293,284
3. U.S. Patent No. 8,282,966
4. U.S. application serial no. 13/683,417

Electronic Patent Application Fee Transmittal	
Application Number:	13683236
Filing Date:	21-Nov-2012
Title of Invention:	METHODS OF DISTRIBUTING A PHARMACEUTICAL PRODUCT COMPRISING NITRIC OXIDE GAS FOR INHALATION
First Named Inventor/Applicant Name:	James S. Baldassarre
Filer:	Janis K. Fraser/Christine Grace
Attorney Docket Number:	26047-0003006
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($)
Miscellaneous:				
Statutory or Terminal Disclaimer	1814	4	160	640
		Total in USD ($)		**640**

Electronic Acknowledgement Receipt	
EFS ID:	19637441
Application Number:	13683236
International Application Number:	
Confirmation Number:	5655
Title of Invention:	METHODS OF DISTRIBUTING A PHARMACEUTICAL PRODUCT COMPRISING NITRIC OXIDE GAS FOR INHALATION
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:	26047-0003006
Receipt Date:	21-JUL-2014
Filing Date:	21-NOV-2012
Time Stamp:	17:15:05
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$640
RAM confirmation Number	4325
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		Response.pdf	63902 75bfe7098c63a80552662d1f89c3f88bb64d1f4f	yes	2
	Multipart Description/PDF files in .zip description				
	Document Description		**Start**	**End**	
	Response After Final Action		1	1	
	Applicant Arguments/Remarks Made in an Amendment		2	2	
Warnings:					
Information:					
2	Terminal Disclaimer Filed	TD.pdf	77319 50e7fa7bd1ad9b471c84e477e592dc1e621b5416	no	3
Warnings:					
Information:					
3	Fee Worksheet (SB06)	fee-info.pdf	30337 037292ca4a296c634f3e8e61a691c0699c0b0819	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	171558		

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	
	13/683,236	BALDASSARRE, JAMES S.	

Document Code - DISQ	Internal Document – DO NOT MAIL

TERMINAL DISCLAIMER	☒ APPROVED	☐ DISAPPROVED
Date Filed : 7/21/14	This patent is subject to a Terminal Disclaimer	

Approved/Disapproved by:
Janice Ford

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 07/31/2014

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

EXAMINER
ARNOLD, ERNST V

ART UNIT	PAPER NUMBER
1613	

DATE MAILED: 07/31/2014

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/683,236	11/21/2012	James S. Baldassarre	26047-0003006	5655

TITLE OF INVENTION: METHODS OF DISTRIBUTING A PHARMACEUTICAL PRODUCT COMPRISING NITRIC OXIDE GAS FOR INHALATION

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$960	$0	$0	$960	10/31/2014

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 07/31/2014
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.
13/683,236	11/21/2012	James S. Baldassarre	26047-0003006	5655

TITLE OF INVENTION: METHODS OF DISTRIBUTING A PHARMACEUTICAL PRODUCT COMPRISING NITRIC OXIDE GAS FOR INHALATION

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$960	$0	$0	$960	10/31/2014

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

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.
13/683,236	11/21/2012	James S. Baldassarre	26047-0003006	5655

94169 7590 07/31/2014

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

EXAMINER	
ARNOLD, ERNST V	
ART UNIT	PAPER NUMBER
1613	

DATE MAILED: 07/31/2014

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. 13/683,236	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 *7/21/14*.
   ☐ 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, 6-10, 21, 25, 26 and 31-40*. 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 **T**HREE MON**T**HS FROM **T**HE "MAILING DA**T**E" 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. ☐ CORREC**T**ED 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 REQUIREMEN**T** FOR **T**HE DEPOSI**T** OF BIOLOGICAL MA**T**ERIAL.

Attachment(s)

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

/ERNST V ARNOLD/
Primary Examiner, Art Unit 1613

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

DETAILED ACTION

Claims 1, 6-10, 21, 25, 26 and 31-40 are pending and under examination.

Withdrawn rejections:

Applicant's amendments and arguments filed 7/21/14 are acknowledged and have been fully considered. The Examiner has re-weighed all the evidence of record. Any rejection and/or objection not specifically addressed below is herein withdrawn.

Terminal Disclaimer

The terminal disclaimer filed on 7/21/14 disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of US Patent Numbers 8431163, 8293284, 8282966 and US application number 13683417 has been reviewed and is accepted. The terminal disclaimer has been recorded.

Allowable Subject Matter

The following is an examiner's statement of reasons for allowance: Applicant's terminal disclaimer has been approved and there are no remaining issues. The instantly claimed subject is allowed for the reasons of record.

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, 6-10, 21, 25, 26 and 31-40, renumbered as 1-19, are allowed.

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

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

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

/ERNST V ARNOLD/
Primary Examiner, Art Unit 1613

OK to Enter
/EA/
7/29/14

Attorney Docket No.: 26047-0003006 / Client Ref: 3000-US-0008DIV

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Named Inventor	:	James S. Baldassarre	Art Unit	:	1613
Serial No.	:	13/683,236	Examiner	:	Ernst V. Arnold
Filed	:	November 21, 2012	Conf. No.	:	5655
Title	:	METHODS OF DISTRIBUTING A PHARMACEUTICAL PRODUCT COMPRISING NITRIC OXIDE GAS FOR INHALATION			

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

REPLY TO FINAL ACTION OF JULY 16, 2014

In response to the Final Action, please consider the following remarks.

EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	4	"8431163".pn.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2014/07/27 11:48
L2	7	(("424/718" or 128/200.24 or 423/405).ccls. and (((nitric adj oxide) or (nitrogen adj monoxide)) and (LVD or (left with dysfunction)) and (neonatal or neonate or newborn)).clm.)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2014/07/27 12:07
S1	1	"20100330206".pn. and ((supply or supplying) and (medical adj provider) and responsible)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2013/04/12 14:50
S2	1	"20100330206".pn. and ((supply or supplying) and (medical adj provider) and responsible and (delivery with device))	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2013/04/12 14:51
S3	0	"20100330206".pn. and (source with ((compressed adj gas) or (delivery adj devicd)))	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2013/04/12 14:52
S4	1	"20100330206".pn. and (source with ((compressed adj gas) or (delivery adj device)))	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2013/04/12 14:52
S5	1	"20130078321".pn. and (source with ((compressed adj gas) or (delivery adj device)))	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2013/04/12 14:54
S6	1	"20100330206".pn. and ((compressed adj gas) or (delivery adj device))	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2013/04/12 14:57
S7	1	"20100331405".pn. and ((compressed adj gas) or (delivery adj device))	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2013/04/12 14:59
S8	0	"20130078321".pn. and (distribute or distributing)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2013/04/12 15:24

S9	0	"20100331405".pn. and (distribute or distributing)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2013/04/12 15:26
S10	0	"8431163".pn. and (distribute or distributing)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2013/04/12 15:28
S11	0	"20100330206".pn. and (distribute or distributing)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2013/04/12 15:29
S12	0	"13683236" and benefit and outweigh and potential	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2013/04/20 10:45
S13	1	"13683236" and (benefit with potential)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2013/04/20 10:45
S14	42	baldassarre.in. and (generate or generated or generating)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2014/02/03 09:14
S15	0	baldassarre.in. and ((generate or generated or generating) with cylinder)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2014/02/03 09:15
S16	1	baldassarre.in. and ((warn or warning) with (first or second))	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2014/02/03 09:28
S17	1	"12820866" and ((warn or warning) with (first or second))	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2014/02/03 09:31
S18	4	"12820866"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2014/02/03 09:31
S19	7	"12821041"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2014/02/03 11:39
S20	2	"12821041" and (warn or warning)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2014/02/03 11:40

S21	1	"13683236"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2014/02/03 15:09

EAST Search History (Interference)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L3	7	(("424/718" or 128/200.24 or 423/405).ccls. and (((nitric adj oxide) or (nitrogen adj monoxide)) and (LVD or (left with dysfunction)) and (neonatal or neonate or newborn)).clm.)	US-PGPUB; USPAT; UPAD	OR	ON	2014/07/27 12:07
L4	3	(A01N59/00 and (((nitric adj oxide) or (nitrogen adj monoxide)) and (LVD or (left with dysfunction)) and (neonatal or neonate or newborn)).clm.)	US-PGPUB; USPAT; UPAD	OR	ON	2014/07/27 12:08
L5	8	(A61K33/00 and (((nitric adj oxide) or (nitrogen adj monoxide)) and (LVD or (left with dysfunction)) and (neonatal or neonate or newborn)).clm.)	US-PGPUB; USPAT; UPAD	OR	ON	2014/07/27 12:08
L6	3	(C01B21/24 and (((nitric adj oxide) or (nitrogen adj monoxide)) and (LVD or (left with dysfunction)) and (neonatal or neonate or newborn)).clm.)	US-PGPUB; USPAT; UPAD	OR	ON	2014/07/27 12:08
L7	3	(A61M16/00 and (((nitric adj oxide) or (nitrogen adj monoxide)) and (LVD or (left with dysfunction)) and (neonatal or neonate or newborn)).clm.)	US-PGPUB; USPAT; UPAD	OR	ON	2014/07/27 12:09

7/27/2014 12:09:25 PM
C:\Users\earnold\Documents\EAST\Workspaces\13683236.wsp

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13683236	BALDASSARRE ET AL.
	Examiner	Art Unit
	ERNST ARNOLD	1613

CPC- SEARCHED		
Symbol	Date	Examiner
A01N 59/00 text limited	7/27/14	eva
A61K 33/00 text limited	7/27/14	eva
C01B 21/24 text limited	7/27/14	eva
A61M 16/00 text limited	7/27/14	eva

CPC COMBINATION SETS - SEARCHED		
Symbol	Date	Examiner

US CLASSIFICATION SEARCHED			
Class	Subclass	Date	Examiner
424	718	7/27/14	eva
128	200.24	7/27/14	eva
423	405	7/27/14	eva

SEARCH NOTES		
Search Notes	Date	Examiner
consultation with QAS Majorie Moran on 101 issues and drafting of rejection	12/21/12	eva
consultation with TC1600 MMoran on 101 issues and claim rejections	4/19/13	eva
search update EAST all databases	4/22/13	eva
consult SPE BKwon and SPE JVollano on priority date	2/4/14	eva
search update	2/4/14	eva
updated IDS	7/11/14	eva
search update EAST	7/27/14	eva

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

INTERFERENCE SEARCH			
US Class/ CPC Symbol	**US Subclass / CPC Group**	**Date**	**Examiner**
424	718 text limited	7/27/14	eva
128	200.24 text limited	7/27/14	eva
423	405 text limited	7/27/14	eva

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13683236	BALDASSARRE, JAMES S.
	Examiner	Art Unit
	ERNST V ARNOLD	1613

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

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

CLAIM		DATE								
Final	Original	07/27/2014								
	1	=								
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	29									
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	31	=								
	32	=								
	33	=								
	34	=								
	35	=								
	36	=								

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13683236	BALDASSARRE, JAMES S.
	Examiner	Art Unit
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CLAIM		DATE								
Final	Original	07/27/2014								
	37	=								
	38	=								
	39	=								
	40	=								

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BIB DATA SHEET

CONFIRMATION NO. 5655

SERIAL NUMBER	FILING or 371(c) DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
13/683,236	11/21/2012 RULE	424	1613	26047-0003006

APPLICANTS
INO THERAPEUTICS LLC, Hampton, NJ

INVENTORS
James S. Baldassarre, Doylestown, PA;

**** CONTINUING DATA ***************************
This application is a DIV of 12/820,866 06/22/2010 ABN
which is a CON of 12/494,598 06/30/2009 ABN
This application 13/683,236 11/21/2012
is a DIV of 13/651,660 10/15/2012 PAT 8431163
which is a CON of 12/821,041 06/22/2010 PAT 8293284
which is a CON of 12/494,598 06/30/2009 ABN

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

**** IF REQUIRED, FOREIGN FILING LICENSE GRANTED ****
12/04/2012

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	19 ~~30~~	4

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

TITLE
METHODS OF DISTRIBUTING A PHARMACEUTICAL PRODUCT COMPRISING NITRIC OXIDE GAS FOR INHALATION

FILING FEE RECEIVED		
2430	FEES: Authority has been given in Paper No._____ to charge/credit DEPOSIT ACCOUNT No._____ for following:	☐ All Fees ☐ 1.16 Fees (Filing) ☐ 1.17 Fees (Processing Ext. of time) ☐ 1.18 Fees (Issue) ☐ Other _____ ☐ Credit

BIB (Rev. 05/07).

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13683236	BALDASSARRE, JAMES S.
	Examiner	**Art Unit**
	ERNST V ARNOLD	1613

CPC						
Symbol					**Type**	**Version**
A61K		31	/	21	I	2013-01-01
A61B		8	/	48	I	2013-01-01
A61M		16	/	12	I	2013-01-01
A61K		45	/	06	I	2013-01-01
A61K		33	/	00	F	2013-01-01
G06Q		99	/	00	I	2013-01-01
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CPC Combination Sets								
Symbol					**Type**	**Set**	**Ranking**	**Version**
A61K		2300	/	00	A	2	2	2013-01-01
A61K		31	/	21	I	1	1	2013-01-01
A61K		33	/	00	I	2	1	2013-01-01
A61K		2300	/	00	A	1	2	2013-01-01

NONE		**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	19	
/ERNST V ARNOLD/ Primary Examiner.Art Unit 1613	7/27/14	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	none

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13683236	BALDASSARRE, JAMES S.
	Examiner	**Art Unit**
	ERNST V ARNOLD	1613

US ORIGINAL CLASSIFICATION		INTERNATIONAL CLASSIFICATION														
CLASS	SUBCLASS	CLAIMED					NON-CLAIMED									
424	718	A	0	1	N	59 / 00 (2006.01.01)										
CROSS REFERENCE(S)		C	0	1	B	21 / 24 (2006.01.01)										
		A	6	1	M	16 / 00 (2006.01.01)										
CLASS	SUBCLASS (ONE SUBCLASS PER BLOCK)															
128	200.24															
423	405															

NONE		Total Claims Allowed:	
(Assistant Examiner)	(Date)	19	
/ERNST V ARNOLD/ Primary Examiner.Art Unit 1613	7/27/14	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	none

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

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

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

NONE (Assistant Examiner)	(Date)	**Total Claims Allowed:** 19	
/ERNST V ARNOLD/ Primary Examiner.Art Unit 1613 (Primary Examiner)	7/27/14 (Date)	O.G. Print Claim(s) 1	O.G. Print Figure none

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/683,236	11/21/2012	James S. Baldassarre	26047-0003006	5655

94169 7590 08/19/2014
Fish & Richardson PC
P.O.Box 1022
minneapolis, MN 55440

EXAMINER	
ARNOLD, ERNST V	
ART UNIT	PAPER NUMBER
1613	
MAIL DATE	DELIVERY MODE
08/19/2014	PAPER

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

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U.S. Patent and Trademark Office
Address : COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450

APPLICATION NO./ CONTROL NO.	FILING DATE	FIRST NAMED INVENTOR / PATENT IN REEXAMINATION	ATTORNEY DOCKET NO.
13/683,236	21 November, 2012	BALDASSARRE, JAMES S.	26047-0003006

		EXAMINER	
Fish & Richardson PC P.O.Box 1022 minneapolis, MN 55440		ERNST V. ARNOLD	
		ART UNIT	PAPER
		1613	20140818

DATE MAILED:

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

Commissioner for Patents

Applicant notified the Examiner that the IDS filed 12/7/12 did not have the "all references considered" statement at the bottom. This communication and attached IDS with the "all references considered" statement correct that deficiency. No response from Applicant is required.

/ERNST V ARNOLD/
Primary Examiner, Art Unit 1613

PTO-90C (Rev.04-03)

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99)**		
	Application Number	13683236
	Filing Date	2012-11-21
	First Named Inventor	Baldassarre
	Art Unit	
	Examiner Name	
	Attorney Docket Number	26047-0003006

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

Receipt date: 12/07/2012	Application Number	13683236	13683236 - 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	26047-0003006	

	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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Receipt date: 12/07/2012	Application Number	13683236	13683236 - 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	26047-0003006	

	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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Receipt date: 12/07/2012	Application Number	13683236 13683236 - 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	
	Examiner Name	
	Attorney Docket Number	26047-0003006

	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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Receipt date: 12/07/2012	Application Number	13683236 13683236 - 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	26047-0003006

	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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Receipt date: 12/07/2012	Application Number	13683236 13683236 - 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	26047-0003006

	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	/Ernst Arnold/	Date Considered	12/31/2012

*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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Receipt date: 12/07/2012	Application Number	13683236	13683236 - 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	26047-0003006	

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.**

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

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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./

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 07/31/2014

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.
13/683,236	11/21/2012	James S. Baldassarre	26047-0003006	5655

TITLE OF INVENTION: METHODS OF DISTRIBUTING A PHARMACEUTICAL PRODUCT COMPRISING NITRIC OXIDE GAS FOR INHALATION

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	SMALL	$480	$0		$480	10/31/2014

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 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, New Jersey

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.

[X] 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 August 20, 2014

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

23276352.doc

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Named Inventor	:	James S. Baldassarre	Art Unit	:	1613
Serial No.	:	13/683,236	Examiner	:	Ernst V. Arnold
Filed	:	November 21, 2012	Confirmation No.	:	5655
			Notice of Allowance Date: July 31, 2014		
Title	:	METHODS OF DISTRIBUTING A PHARMACEUTICAL PRODUCT COMPRISING NITRIC OXIDE GAS FOR INHALATION			

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

REPLY TO NOTICE OF ALLOWANCE

In response to the Notice of Allowance mailed July 31, 2014, enclosed is a completed Part B - Fee(s) Transmittal.

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

Respectfully submitted,

Date: August 20, 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

23276348.doc

Electronic Patent Application Fee Transmittal	
Application Number:	13683236
Filing Date:	21-Nov-2012
Title of Invention:	METHODS OF DISTRIBUTING A PHARMACEUTICAL PRODUCT COMPRISING NITRIC OXIDE GAS FOR INHALATION
First Named Inventor/Applicant Name:	James S. Baldassarre
Filer:	Janis K. Fraser/Christine Grace
Attorney Docket Number:	26047-0003006
Filed as Small Entity	

Utility under 35 USC 111(a) Filing Fees

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

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

Electronic Acknowledgement Receipt	
EFS ID:	19917140
Application Number:	13683236
International Application Number:	
Confirmation Number:	5655
Title of Invention:	METHODS OF DISTRIBUTING A PHARMACEUTICAL PRODUCT COMPRISING NITRIC OXIDE GAS FOR INHALATION
First Named Inventor/Applicant Name:	James S. Baldassarre
Customer Number:	94169
Filer:	Janis K. Fraser/Brenda Jurgens
Filer Authorized By:	Janis K. Fraser
Attorney Docket Number:	26047-0003006
Receipt Date:	20-AUG-2014
Filing Date:	21-NOV-2012
Time Stamp:	16:09:43
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$480
RAM confirmation Number	2434
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)	85b.pdf	107628 2fbc82b5d93ba3a2deaa7f02be5fc120cb929415	no	1
Warnings:					
Information:					
2	Post Allowance Communication - Incoming	Response.pdf	62433 6037294445e016082f00a81fea4494b7e1974934	no	1
Warnings:					
Information:					
3	Fee Worksheet (SB06)	fee-info.pdf	30409 f36b70dbd3ca70d28f06bd8ab86d905affa30545	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	200470		

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

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

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

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

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/683,236	09/30/2014	8846112	26047-0003006	5655

94169 7590 09/10/2014

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:	Mail Stop 8 Director of the U.S. Patent and Trademark Office P.O. Box 1450 Alexandria, VA 22313-1450	REPORT ON THE FILING OR DETERMINATION OF AN ACTION REGARDING A PATENT OR TRADEMARK

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
Tel: 571-272-7822

Paper 12
Entered: July 29, 2015

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

PRAXAIR DISTRIBUTION, INC.,
Petitioner,
v.
INO THERAPEUTICS LLC,
Patent Owner.

Case IPR2015-00529
Patent 8,846,112 B2

Before LORA M. GREEN, TINA E. HULSE,
and ROBERT A. POLLOCK, *Administrative Patent Judges.*

POLLOCK, *Administrative Patent Judge.*

DECISION
Institution of *Inter Partes* Review
37 C.F.R. § 42.108

I. INTRODUCTION

Petitioner, Praxair Distribution, Inc., filed a Petition (Paper 1; "Pet.") to institute an *inter partes* review of claims 1–19 of U.S. Patent No. 8,846,112 B2 (Ex. 1001; "the '112 patent"). Patent Owner, INO Therapeutics LLC (d/b/a, Ikaria[1]), filed a Patent Owner Preliminary Response. Paper 8 ("Prelim. Resp.").

We have jurisdiction under 35 U.S.C. § 314. The standard for instituting an *inter partes* review, set forth in 35 U.S.C. § 314(a), states that an *inter partes* review may not be instituted unless "the information presented in the [Petition and Preliminary Response] shows that there is a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition." Upon considering the instant Petition and Preliminary Response, we conclude that Petitioner has established that there is a reasonable likelihood that it would prevail with respect to at least one of the challenged claims. Accordingly, institution of an *inter partes* review as to claims 1–19 of the '112 patent is authorized.

A. Related Proceedings

Petitioner states that on February 19, 2015, Patent Owner filed a complaint in the United States District Court for the District of Delaware averring that Petitioner's Abbreviated New Drug Application infringes the '112 patent under 35 U.S.C. § 271(e)(2), and that the lawsuit is pending under the caption: *INO Therapeutics LLC v. Praxair Distribution, Inc.*, Civil Action No. 1:15-cv-00170 (GMS). Paper 7.

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[1] Patent Owner's Amended Mandatory Notice Under 37 C.F.R. § 42.8(a)(3) identifies "Mallinckrodt PLC, successor-in-interest of Ikaria, Inc., and affiliate of INO Therapeutics LLC, as a real party-in-interest." Paper 10.

In addition to the case before us, Petitioner has requested *inter partes* review of Ikaria patents in the following matters:

A) Case No. IPR2015-00522 (U.S. Patent No. 8,282,966)

B) Case No. IPR2015-00524 (U.S. Patent No. 8,293,284)

C) Case No. IPR2015-00525 (U.S. Patent No. 8,431,163)

D) Case No. IPR2015-00526 (U.S. Patent No. 8,795,741)

E) Case No. IPR2015-00884 (U.S. Patent No. 8,291,904)

F) Case No. IPR2015-00888 (U.S. Patent No. 8,776,794)

G) Case No. IPR2015-00889 (U.S. Patent No. 8,573,209)

H) Case No. IPR2015-00891 (U.S. Patent No. 8,573,210)

I) Case No. IPR2015-00893 (U.S. Patent No. 8,776,795)

The patents at issue in matters A) through D) have substantially the same specification as the '112 patent at issue here, and are generally directed to methods of administering inhaled nitric oxide to neonates. The patents at issue in matters E) through I) are part of a separate family of patents, and are generally directed to devices suitable for the delivery of nitric oxide gas.

B. The '112 Patent

Nitric oxide is a lung-specific vasodialator that significantly improves blood oxygenation and reduces the need for extracorporeal oxygenation. Ex. 1001, 3:36–45, 7:1–29. INOmax® is an FDA-approved blend of nitric oxide and nitrogen, which may be administered in conjunction with ventilary support and oxygen for iNO (inhaled nitric oxide) therapy. *Id.* at 1:20–25, 3:34–36, 3:57–62. The product is approved "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, a condition also known as

persistent pulmonary hypertension in the newborn (PPHN)." *Id.* at 6:34–40. iNO has also been used for a variety of other conditions, where it generally "acts by preventing or treating reversible pulmonary vasoconstriction, reducing pulmonary arterial pressure and improving pulmonary gas exchange." *Id.* at 6:40–52.

Example 1 of the Specification discusses the conduct and results of the INOT22 Study, in which children undergoing cardiac catheterization were administered oxygen, oxygen in conjunction with iNO, or iNO alone. *Id.* at 9:35–10:27. The Specification states that "[i]dentifying patients with pre-existing LVD [left ventricular dysfunction] 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 electrocardiography diagnostic screening." *Id.* at 5:15–19. During the INOT22 study, patients with pre-existing LVD experienced an increased rate of serious adverse events (SAEs) including pulmonary edema. *See, e.g.*, *id.* at 9:47–51, 14:17–25. In an effort to minimize the risk of adverse events, the INOT22 protocol was amended to exclude patients with an elevated pulmonary capillary wedge pressure (PCWP). *See id.* at 14:17–25. PCWP is a measure of left atrial pressure that may be used to diagnose LVD. *Id.* at 5:20–28. The Specification states, for example:

> 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.

Id. at 12:47–61. In light of the above results indicating that iNO therapy may be detrimental to patients with pre-existing LVD, the Specification proposes amending the INOmax® prescribing information to include a precaution for patients with LVD. *Id.* at 9:51–53.

C. Representative Claim

The independent claims at issue, claims 1, 7, 12, and 14 of the '112 patent, involve "supplying [a] cylinder containing compressed nitric oxide gas to a medical provider" in conjunction with "information that, in patients with pre-existing left ventricular dysfunction, inhaled nitric oxide may increase pulmonary capillary wedge pressure (PCWP) leading to pulmonary edema." Claim 1, reproduced below and formatted for clarity, is illustrative:

> 1. A method of providing pharmaceutically acceptable nitric oxide gas the method comprising:
> obtaining a cylinder containing compressed nitric oxide gas in the form of a gaseous blend of nitric oxide and nitrogen:
> supplying the cylinder containing compressed nitric oxide gas to a medical provider responsible for treating neonates who have hypoxic respiratory failure, including some who do not have left ventricular dysfunction;
> providing to the medical provider
> (i) information that a recommended dose of inhaled nitric oxide gas for treatment of neonates with hypoxic respiratory failure is 20 ppm nitric oxide and
> (ii) information that, in patients with pre-existing left ventricular dysfunction, inhaled nitric oxide may increase pulmonary capillary wedge pressure (PCWP), leading to pulmonary edema,
> the information of (ii) being sufficient to cause a medical provider considering inhaled nitric oxide treatment for a

> plurality of neonatal patients who (a) are suffering from a condition for which inhaled nitric oxide is indicated, and (b) have pre-existing left ventricular dysfunction, to elect to avoid treating one or more of the plurality of patients with inhaled nitric oxide in order to avoid putting the one or more patients at risk of pulmonary edema.

D. The Prior Art and Supporting Evidence

Pursuant to 37 C.F.R. § 42.104(b), Petitioner identifies the following prior art as the basis of challenging claims 1–19 of the '112 patent. *See* Pet. v–x, 8.

A. Bernasconi & M. Beghetti, *Inhaled Nitric Oxide Applications in Paediatric Practice*, 4 IMAGES IN PAEDIATRIC CARDIOLOGY 4 (2002). Ex. 1004 ("Bernasconi").

Evan Loh et al., *Cardiovascular Effects of Inhaled Nitric Oxide in Patients with Left Ventricular Dysfunction*, 90 CIRCULATION 2780 (1994). Ex. 1006 ("Loh").

P. Goyal, et al., *Efficacy of Nitroglycerin Inhalation in Reducing Pulmonary Arterial Hypertension in Children with Congenital Heart Disease*, 97 BRITISH JOURNAL OF ANAESTHESIA 208 (2006). Ex. 1007 ("Goyal").

Fumito Ichinose et al., *Inhaled Nitric Oxide: A Selective Pulmonary Vasodilator: Current Uses and Therapeutic Potential*, 109 CIRCULATION 3106 (2004). Ex. 1009 ("Ichinose").

The Neonatal Inhaled Nitric Oxide Study Group, *Inhaled Nitric Oxide in Full-Term and Nearly Full-Term Infants with Hypoxic Respiratory Failure*, 336 THE NEW ENGLAND JOURNAL OF MEDICINE 597 (1997). Ex. 1011 ("Neonatal Group").

Center for Drug Evaluation and Research, Application Number: NDA 20845, INOmax™, Final Printed Labeling, *available at* http://www.accessdata.fda.gov/drugsatfda_docs/nda/99/20845_INOmax_prntlbl.pdf (August 9, 2000). Ex. 1014 ("INOmax label").

Petitioner further relies on the Declaration of Dr. Maurice Beghetti (Ex. 1002), the prosecution history of the '112 patent (Ex. 1056), and a number of

supplementary references, which are discussed herein only to the extent they provide relevant background or clarification of the asserted references.

E. Asserted Grounds of Unpatentability

Petitioner challenges claims 1–19 of the '112 patent on the following grounds. Pet. 8, 18–55.

References	Basis	Claims Challenged
Bernasconi, INOmax label, Loh, and Goyal	§ 103(a)	1–19
Ichinose, INOmax label, Loh, Neonatal Group, and Goyal	§ 103(a)	1–19

II. ANALYSIS

A. Claim Interpretation

In an *inter partes* review, the Board interprets claim terms in an unexpired patent according to their broadest reasonable construction in light of the specification of the patent in which they appear. 37 C.F.R. § 42.100(b); *see In re Cuozzo Speed Techs., LLC*, No. 2014-1301, 2015 WL 4097949, at *5–*8 (Fed. Cir. July 8, 2015). Under this standard, claim terms are given their ordinary and customary meaning, as would be understood by one of ordinary skill in the art in the context of the entire disclosure. *In re Translogic Tech., Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007). Nevertheless, a "claim term will not receive its ordinary meaning if the patentee acted as his own lexicographer and clearly set forth a definition of the disputed claim term in either the specification or prosecution history." *CCS Fitness, Inc. v. Brunswick Corp.*, 288 F.3d 1359, 1366 (Fed. Cir. 2002). Such definitions must be set forth with reasonable clarity, deliberateness, and precision. *In re Paulsen*, 30 F.3d 1475, 1480 (Fed. Cir. 1994).

Petitioner asserts that all claim terms should be accorded their plain and ordinary meanings. Pet. 8. Patent Owner "agrees that the plain and ordinary meaning should apply where the patentee has not acted as his own lexicographer." Prelim. Resp. 21. We provide express constructions for the following terms.

1. "Near Term Neontates," "Full Term Infant," and "Neonate"

Patent Owner contends that "near term neonates" are defined in the Specification as "those having achieved '>34 weeks gestation.'" *Id.* (citing Ex. 1001, 6:34–36) *see also* Ex. 1014, 4 ("near-term (>34 weeks) neonates"). Patent Owner further contends that Stedman's Medical Dictionary[2] evidences the common and ordinary meaning of "full term infant" as one with a "gestational age between 37 completed weeks (259 completed days) and 42 completed weeks (294 completed days)," and "neonate" as "an infant aged 1 month or younger; newborn." Prelim. Resp. 21–22 (citing Ex. 2007, 968, 1288). Absent evidence or argument to the contrary, on the current record, we adopt the Patent Owner's proposed meaning as the broadest reasonable interpretations of these terms .

2. "Providing . . . Information"

Independent claim 1 includes the step of providing to a medical provider

> (i) information that a recommended dose of inhaled nitric oxide gas for treatment of neonates with hypoxic respiratory failure is 20 ppm nitric oxide and
> (ii) information that, in patients with pre-existing left ventricular dysfunction, inhaled nitric oxide may increase pulmonary capillary wedge pressure (PCWP), leading to pulmonary edema
> the information of (ii) being sufficient to cause a medical provider considering inhaled nitric oxide treatment for a

[2] Stedman's Medical Dictionary 967–68 (28th ed. 2006).

> plurality of neonatal patients who (a) are suffering from a condition for which inhaled nitric oxide is indicated, and (b) have pre-existing left ventricular dysfunction, to elect to avoid treating one or more of the plurality of patients with inhaled nitric oxide in order to avoid putting the one or more patients at risk of pulmonary edema.

Claim 5, depending from claim 1, expressly provides that the information "appear[s] in prescribing information supplied to the medical provider with the cylinder containing compressed nitric oxide gas," e.g., a version of the FDA-approved labling for INOmax®, Ex. 1004. Accordingly, we view the information described in (i) and (ii) as tantamount to printed matter.[3]

Because printed matter itself is non-statutory subject matter, it must have a functional relationship to other claim elements to be accorded patentable weight. *See In re Miller*, 418 F.2d 1392, 1396 (CCPA 1969); *see also In re Ngai*, 367 F.3d 1336, 1339 (Fed. Cir. 2004) ("If we were to adopt Ngai's position, anyone could continue patenting a product indefinitely provided that they add a new instruction sheet to the product."). Expressly extending the printed matter doctrine to method claims, the Federal Circuit in *King Pharmaceuticals* found that an otherwise anticipated method claim did not become patentable because it included "a step of 'informing' someone about the existence of an inherent property of that method." *King Pharms., Inc. v. Eon Labs, Inc.*, 616 F.3d 1267, 1278 (Fed. Cir. 2010); *see id* at 1277 (claim 21 reciting "informing the patient that administration of a therapeutically effective amount of metaxalone in a pharmaceutical composition with food results in an increase in the maximal plasma concentration (Cmax) and extent of absorption (AUC(last)) of metaxalone compared to administration

[3] We apply the same analysis to the "providing" step of independent claims 12 and 14, which recite similarly-worded information (i) and (ii).

without food"). The court expressly rejected the argument that a functional relationship exists between the step of taking metaxalone with food and the "informing" limitation because that limitation "increases the likelihood that the patient will take metaxalone with food, thereby increasing the efficiency of the method." *Id.* at 1279. According to the court, this relationship is not functional:

> Informing a patient about the benefits of a drug in no way transforms the process of taking the drug with food. Irrespective of whether the patient is informed about the benefits, the actual method, taking metaxalone with food, is the same. In other words, the "informing" limitation "in no way depends on the [method], and the [method] does not depend on the ['informing' limitation]." *In re Ngai,* 367 F.3d at 1339 (alterations added). "It is not invention to perceive that the product which others had discovered had qualities they failed to detect." *Gen. Elec. Co. v. Jewel Incandescent Lamp Co.,* 326 U.S. 242, 249, 66 S.Ct. 81, 90 L.Ed. 43 (1945).

Id.

In the present case, a cylinder containing compressed nitric oxide gas can be obtained and supplied to a medical provider with, or without, the information recited in (i) and (ii). Because the "method of providing pharmaceutically acceptable nitric oxide gas" can be performed irrespective of whether that knowledge is conveyed, we find that the step of "providing . . . information" lacks a functional relationship to the remaining claim elements, and, therefore, accord it no patentable weight.

That the information of (ii) may be medically important ("sufficient to cause a medical provider . . . to elect to avoid treating one or more [] patients") does not change our analysis, because the finding that inhaled nitric oxide may place a subset of neonatal patients at risk of pulmonary edema is an inherent property of administering the drug to neonates. As in *King Pharmaceuticals*, claim 1 does not become patentable merely "because it includes 'a step of "informing" someone

about the existence of an inherent property of that method.'"[4] *King Pharms.*, 616 F.3d at 1278. "Irrespective of whether the [provider] is informed about the [risks], the actual method, [providing pharmaceutically acceptable nitric oxide gas], is the same." *See id.* at 1280.

3. "Providing . . . a Recommendation"

The remaining independent claim, claim 7, recites providing similarly-worded information as (i) and (ii) of claim 1, as well as "(iii) a recommendation that if pulmonary edema occurs in a patient who has pre-existing left ventricular dysfunction and is treated with inhaled nitric oxide, the treatment with inhaled nitric oxide should be discontinued." For the reasons set forth with respect to information (i) and (ii) of claim 1, provided information (iii) also has no functional relationship to the remaining claim elements. Irrespective of the patient's response, claim 7 merely instructs "obtaining a cylinder containing compresed nitric oxide" and "supplying the cylinder [] to a medical provider."[5]

4. Discontinuing Treatment in Accordance with a Reccomendation

Depending from claim 7, claim 9 recites:

> treating the neonatal patient with 20 ppm inhaled nitric oxide, whereupon the neonatal patient experiences pulmonary edema; and

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[4] For the same reasons, we do not accord patentable weight to the method by which the information is provided, e.g., by "appear[ing] in the prescribing information supplied to the medical provider," as set forth in claims 2, 5, 6, 8, 13, and 15.

[5] We further note that none of the independent claims at issue (claims 1, 7, 12, and 14) requires treating a patient with the inhaled nitric oxide. The absence of any administration step further underscores the lack of a functional relationship between providing information (i), (ii), or (iii) and other claim steps.

> *in accordance with the recommendation of (iii)*, discontinuing the treatment with inhaled nitric oxide due to the neonatal patient's pulmonary edema.

Applying the broadest reasonable interpretation consistant with the Specification, we define "in accordance" to mean "in agreement."[6] That a decision may be in agreement with the recommendation of (iii) fails to modify the step of "discontinuing the treatment with inhaled nitric oxide due to the neonatal patient's pulmonary edema," and is entitled to no patentable weight.

5. Conducting a Risk/Benefit Analyses

Claims 3 and 16–19 relate to performing a risk/benefit analysis based on information set forth in (ii) in order to arrive at, for example, a treatment decision. The language of claim 3 is representative, reciting the step of

> evaluating the potential benefit of treating the first neonatal patient with 20 ppm inhaled nitric oxide vs. the potential risk that inhaled nitric oxide could cause an increase in PCWP leading to pulmonary edema in patients who have pre-existing left ventricular dysfunction, in order to arrive at a decision of whether or not to treat the first neonatal patient with inhaled nitric oxide.

We construe the above language as a purely mental excercise that does not add to the recited method steps (e.g., "performing at least one diagnostic process") and accord it no weight in our analysis. *See In re Lundberg*, 197 F.2d 336, 339 (CCPA 1952) (claim term "'interpreting the cumulative information thus obtained,' involves a purely mental step which can nowise lend patentability to the claims"); *see also In re Venner*, 262 F.2d 91, 95 (CCPA 1958) (holding that

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[6] *See Accordance Definition*, Merriam-Webster.com, http://www.merriam-webster.com/dictionary/accordance (last accessed June 5, 2015).

"[p]atentability cannot be predicated upon a mental step," where setting time control means depended on mental processes of skilled artisan).

Claim 4 recites "evaluating on a case-by-case basis the potential benefit of treating [a] patient with 20 ppm inhaled nitric oxide vs. the potential risk that inhaled nitric oxide could cause an increase in PCWP, leading to pulmonary edema" and "determining that the potential benefit of the treatment outweighs the potential risk described in the second warning."[7] As with claim 3, these elements describe purely mental steps, which we accord no patentable weight. Consistent with this analysis, we note that the last element of claim 4 recites "treating [at least one patient determined to have pre-existing LVD] with 20ppm inhaled nitric oxide"—a step that need not depend on whether iNO is contraindicated for pediatric patients with LVD or a risk/benefit analysis based on that information.

B. Patentability in View of Bernasconi, INOmax label, Loh, and Goyal

Petitioner contends that the challenged claims would have been obvious in view of Bernasconi, INOmax label, Loh, and Goyal. At a high level of generality, Patent Owner claims this invention as providing information regarding the link between iNO therapy and LVD (e.g., as part of the prescribing information supplied with the drug), such that health care providers may make informed treatment decisions. For the reasons set forth above, we accord these informational and deliberative steps no patentable weight. Accordingly, in this proceeding, we

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[7] Claim 4 depends from claim 1, neither of which expressly defines a "second warning." For the purpose of this analysis, we interpret the "second warning" as information set forth in claim 1, element (ii). *See* claims 16–19 (reciting equivalent languge, but replacing "the second warning" with "the potential risk described in the information of (ii) that inhaled nitric oxide could cause an increase in PCWP, leading to pulmonary edema").

find immaterial Patent Owner's arguments that leading experts in pediatric cardiology did not recognize that iNO therapy should be contraindicated in neonates with pre-existing LVD. *See generally* Prelim. Resp. 6–11, 26–34. As discussed below, the remaining claim elements entail art-recognized practices, such as identifying neonates with and without LVD; identifying neonatal candidates for iNO treatment; and treating those candidates with iNO.

1. Overview of the Asserted References

a. Bernasconi

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, Abstact; *see also* Title ("*Inhaled Nitric Oxide Applications in Paediatric Practice*"). Bernasconi teaches "[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. The reference 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 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.* at 12.

According to Petitioner's declarant, who also is one of the authors of Bernasconi, this passage indicates that it may become necessary to discontinue iNO treatment "depending on how the patient responds based on the results of the 'intensive monitoring.'" Ex. 1002 ¶ 43

b. INOmax Label

INOmax label contains information provided to medical providers (Ex. 1014, i; *see also* Ex. 1002 ¶¶ 30–31 ("prescribing information")) regarding approved iNO uses and contraindications (Ex. 1014, 4, 6; Ex. 1002 ¶¶ 31–38). 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," and "should not be used in the treatment of neonates known to be dependent on right-to-left shunting of blood." Ex. 1014, 4. 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). The INOmax® product is provided as a compressed gaseous mixture of nitric oxide and nitrogen in aluminum cylinders and may be administered using a nitric oxide delivery device (e.g., INOvent system). *Id.* at 6–7. Accordingly, Petitioner contends that INOmax label discloses a method "including obtaining a cylinder of a blend of compressed NO/nitrogen gas and/or a delivery device ('INOvent®') that regulates delivery to a patient for inhalation." Pet. 19–20 (citing Ex. 1014, 1, 6; Ex. 1002 ¶¶ 31–34).

c. Loh and Goyal

Petitioner cites Loh for teaching the measurement of PCWP in conjunction with the iNO treatment in patients with LVD. Pet. 12–13. Petitioner further cites Goyal as teaching the measurement of PCWP in neonates with severe LVD in association with the administration of "a nitric oxide donor drug (i.e. inhaled nitroglycerin)." *Id.* at 13; *see* Ex. 1002 ¶¶ 27, 47–49.

2. Independent Claims 1, 7, 12, and 14

In light of the construction set forth in section II(A), claim 1 is directed to "a method of providing pharmaceutically acceptable nitric oxide gas" comprising: (A) "obtaining a cylinder containing compressed nitric oxide gas in the form of a gaseous blend of nitric oxide and nitrogen" and (B) "supplying the cylinder containing compressed nitric oxide gas to a medical provider responsible for treating neonates who have hypoxic respiratory failure, including some who do not have left ventricular dysfunction." Claims 7, 12, and 14 comprise the same, or essentially the same elements, with claims 12 and 14 further referencing "a device that delivers nitric oxide gas into an inspiratory limb of a breathing circuit." *See also* claims 15, 18, and 19 (referencing a device).

Regarding part (A) of claim 1, Petitioner asserts that INOmax label teaches supplying a cylinder containing a mixture of compressed nitric oxide and nitrogen for the treatment of neonates with hypoxic respiratory failure. Pet. 12, 19; *e.g.*, Ex. 1014, 4, 6–7; *see generally*, Ex. 1002 ¶¶ 30–38. Petitioner also asserts that, with respect to the device recited in claims 12 and 14, INOmax label discloses the INOvent delivery system and other devices to regulate delivery of iNO to the patient. Pet. 12, 19–20; Ex. 1014, 6; Ex. 1002 ¶ 34.

Regarding part (B) of claim 1, Petitioner asserts that INOmax label discloses supplying cylinders of iNO to medical providers who treat neonates with hypoxic respiratory failure. Pet. 12, 20; Ex. 1014, 1, 2, 4, 6–7; Ex. 1002 ¶¶ 31–33, 35–38. With respect to the treatment of "some [patients] who do not have left ventricular dysfunction," as recited in part (B) of the claim, the Specification admits that "[i]dentifying patients with pre-existing LVD is known to those skilled in the medicinal arts." Ex. 1001, 5:15–19. In addition, Petitioner asserts that INOmax label does not draw a distinction between treating neonates with and without LVD and, thus, discloses treating neonates with hypoxic respiratory failure, including those who do not have LVD. Pet. 20–21; Ex. 1002 ¶ 32 (citing Ex. 1014, 4).

Petitioner provides extensive arguments in support of a reason to combine the cited prior art. Pet. 14–19. In short, Petitioner asserts that one of ordinary skill in the art "would have been motivated to combine [the teachings of] these references because they represent information available to practitioners to enable practitioners to identify patients with hypoxic respiratory failure who were candidates for iNO treatment and to consider the risks and potential benefits of iNO treatment for such patients." *Id.* at 14 (citing Ex. 1002 ¶¶ 61–62.) Petitioner relies on the testimony of Dr. Beghetti in asserting that one of ordinary skill in the art "would have referred to *INOMAX label* for FDA-approved aspects of the treatment, and would have found *Bernasconi*, *Loh*, and *Goyal* using known methods to fully understand weighing benefits and risks associated with iNO therapy, with a reasonable expectation of success." *Id.* at 17 (citing Ex. 1002 ¶¶ 72–74.) In addition, Petitioner contends that "a POSA would have been motivated to combine these references because they represent information available to practitioners to enable practitioners to identify patients with hypoxic

respiratory failure who were candidates for iNO treatment and to consider the risks and potential benefits of iNO treatment for such patients." *Id.* at 14 (citing Ex. 1002 ¶¶ 61–62).

In response, Patent Owner relies primarily on expert declarations submitted during the prosecution of the '112 patent as evidence of (1) differences between the etiology and treatment of LVD in children versus adults, and (2) that during the conduct of the INOT22 study, experts in pediatric cardiology were surprised to find that neonates with LVD were at increased risk of serious adverse events. Prelim. Resp. 6–11, 26–31. Accordingly, Patent Owner argues, the ordinary skilled artisan would not have reasonably expected that such patients should be excluded from iNO treatment. *See id.* at 31–34. In light of our determination that the informational and deliberative steps of the challenged claims carry no patentable weight, Patent Owner's arguments are immaterial.

A claim may be anticipated where "each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros., Inc. v. Union Oil Co. of Cal.*, 814 F.2d 628, 631 (Fed. Cir. 1987). As set forth above, Petitioner directs us to INOmax label as disclosing each of the claim features that the panel finds carry patentable weight. In light of the present record, we find that Petitioner is reasonably likely to prevail on an assertion that claims 1, 7, 12, and 14 are unpatentable under 35 U.S.C. § 102(a) as anticipated by INOmax label.

Petitioner has asserted that claims 1, 7, 12, and 14 are unpatentable under 35 U.S.C. § 103(a) as obvious over the combination of INOmax label, Bernasconi, Loh, and Goyal. Petitioner relies on Bernasconi, Loh, and Goyal, however, for features that the panel finds do not have patentable weight. Accordingly, on the

record before us, we conclude that Petitioner has shown a reasonable likelihood that it would prevail on its assertion that claims 1, 7, 12, and 14 are unpatentable under 35 U.S.C. § 103(a) as obvious in light of INOmax label alone. *See In re McDaniel*, 293 F.3d 1379, 1385 (Fed. Cir. 2002) (quoting *Connell v. Sears, Roebuck & Co.*, 722 F.2d 1542, 1548 (Fed. Cir. 1983)) ("It is well settled that 'anticipation is the epitome of obviousness.'"). We, therefore, institute *inter partes* review of claims 1, 7, 12, and 14 under both 35 U.S.C. § 102(a) and 35 U.S.C. § 103(b) grounds in view of INOmax label.

3. Claims 3 and 16

In light of the construction set forth in section II(A), claim 3, depending from claim 1, further comprises the steps of (A) "performing at least one diagnostic process to identify a first neonatal patient who has hypoxic respiratory failure and is a candidate for 20 ppm inhaled nitric oxide treatment;" (B) "determining that the first neonatal patient has pre-existing left ventricular dysfunction;" (C) "identifying a second neonatal patient as having hypoxic respiratory failure and not having left ventricular dysfunction;" and (D) "treating the second neonatal patient with 20 ppm inhaled nitric oxide." Claim 16 recites substantially similar language.

With respect to (A), Petitioner asserts that Bernasconi teaches the use of electrocardiography to diagnose whether a patient had hypoxic respiratory failure and was, thus, a candidate for iNO therapy. Pet. 29; Ex. 1004, 8; Ex. 1002 ¶ 41. Petitioner also asserts that Bernasconi and INOmax label teach that neonatal patients in need of such therapy should be treated with 20 ppm iNO. Pet. 29; Ex. 1004, 6; Ex. 1014, 5; Ex. 1002 ¶ 41.

With respect to (B) and (C), the "[i]dentifying patients with pre-existing

LVD is known to those skilled in the medicinal arts." Ex. 1001, 5:15–19. In addition, Petitioner argues that Bernasconi 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. Pet. 30; Ex. 1002, 8; Ex. 1002 ¶ 42. Petitioner also argues that Loh teaches the determination of pre-existing LVD in adult patients by measuring PCWP in the context of iNO treatment. *See* Pet. 30; Ex. 1002 ¶¶ 46, 47, 69, 77. Petitioner further cites Goyal as teaching the measurement of PCWP in children and neonates. *E.g.*, Pet. 22 (citing Ex. 1007, 209, 210, Table 2; Ex. 1002 ¶¶ 27, 47–48). Insofar as the prior art teaches the identification of patients with LVD, it likewise teaches the identification of those without the condition. With respect to (D), because INOmax label does not draw a distinction between neonates with and without LVD, it, therefore, discloses treating neonates with hypoxic respiratory failure including those without LVD. Ex. 1002 ¶ 32 (citing Ex. 1014, 4).

Accordingly, on the record presently before us, we conclude that Petitioner has shown a reasonable likelihood that it would prevail on its assertion that claims 3 and 16 are unpatentable as obvious over INOmax label, Bernasconi, Loh, and Goyal.

4. Claim 4

In light of the construction set forth in section II(A), claim 4, depending from claim 1, further comprises the steps of: (A) "performing at least one diagnostic process to identify a plurality of neonatal patients who have hypoxic respiratory failure and are candidates for inhaled nitric oxide treatment;" (B) "determining prior to treatment with inhaled nitric oxide whether or not each patient of the plurality has preexisting left ventricular dysfunction;"

(C) "determining that a first patient of the plurality does not have pre-existing left ventricular dysfunction;" (D) "treating the first patient with 20 ppm inhaled nitric oxide;" (E) "determining that other patients of the plurality do have pre-existing left ventricular dysfunction;" and (F) treating the at least one patient with 20 ppm inhaled nitric oxide."

As set forth with respect to claims 1 and 3, above, the combination of the admission of the instant Specification, Bersconi, INOmax label, Loh, and Goyal teach or suggest each step of claim 4. Accordingly, on the record before us, Petitioner has shown a reasonable likelihood that it would prevail on its assertion that claim 4 is unpatentable over the cited art.

5. Claim 9

In light of the construction set forth in section II(A), claim 9, depending from claim 7, recites the steps of: (A) "performing at least one diagnostic process to identify a neonatal patient who has hypoxic respiratory failure and is a candidate for [iNO] treatment;" (B) "determining prior to treatment with [iNO] that the neonatal patient has pre-existing [LVD];" (C) "treating the neonatal patient with 20 ppm [iNO], whereupon the neonatal patient experiences pulmonary edema;" and (D) "discontinuing the treatment with [iNO] due to the neonatal patient's pulmonary edema."

For the purposes of this analysis, steps (A) and (B) of claim 9 have essentially the same scope as steps (A) and (B) of claim 3. With respect to steps (C) and (D), Petitioner argues that Bernasconi teaches the treatment of neonatal patients with 20 ppm iNO. Pet. 34 (citing Ex. 1004, 3, 8); *see* Ex.1014, 6. In addition, the Specification admits that "[i]dentifying patients with pre-existing LVD is known to those skilled in the medicinal arts" (Ex. 1001, 5:15–19), whereas

Petitioner contends that Bernasconi teaches a need for "careful observation and intensive monitoring during [nitric oxide] inhalation" in patients with LVD because iNO may lead to pulmonary edema in such patients. *See* Pet. 11–13, 34; Ex. 1004, 8. As indicated by Petitioner's declarant, the latter teaching suggests to one of ordinary skill in the art that monitoring for pulmonary edema during iNO treatment of LVD patients could result in discontinuing iNO treatment if the patient experienced pulmonary edema. Ex. 1002 ¶ 81.

For the above reasons, we are persuaded, based on the current record, that Petitioner has shown a reasonable likelihood that it would prevail on its assertion that claim 9 is unpatentable over the cited art.

6. Claims 10 and 11

Claim 10, depending from claim 4, further recites that "the at least one patient is monitored for evidence of increased PCWP and/or for evidence of pulmonary edema during treatment with 20 ppm inhaled nitric oxide." Claim 11, depending from claim 7, recites the same language, but expressly defines the patient as a neonatal patient. Petitioner points to Bernasconi as teaching, *inter alia*, that iNO may lead to pulmonary edema in patients with LVD and emphasizes a need for "careful observation and intensive monitoring during [nitric oxide] inhalation" in patients with LVD. Pet. 41; Ex. 1004, 3, 8. Accordingly, based on the current record, we are persuaded that Petitioner has shown a reasonable likelihood that it would prevail on its assertion that claims 10 and 11 are unpatentable over the cited art.

7. Claims 17–19

In light of the construction set forth in section II(A), claim 17 recites that steps of: (A) "identifying a plurality of neonatal hypoxic respiratory failure patients

who are candidates for inhaled nitric oxide treatment;" (B) "determining prior to treatment with inhaled nitric oxide whether or not each patient of the plurality has preexisting left ventricular dysfunction, thereby determining that a first patient of the plurality does not have pre-existing left ventricular dysfunction;" (C) "using the source of nitric oxide gas to treat the first patient with 20 ppm inhaled nitric oxide;" (D) "determining that other patients of the plurality do have pre-existing left ventricular dysfunction;" and (E) "using the source of nitric oxide gas to treat the at least one patient with 20 ppm inhaled nitric oxide."

With respect to (A), the Petition contends that Bernasconi, for example, teaches a diagnostic procedure including electrocardiography to diagnose whether a patient had hypoxic respiratory failure and was thus a candidate for iNO therapy. Pet. 35–36; Ex. 1004, 8; Ex. 1002 ¶¶ 41, 77. Petitioner further contends that Bernasconi and INOmax label teach that neonatal patients in need of such therapy should be treated with 20 ppm iNO. Pet. 36; Ex. 1004, 3, 6, 8, 9; Ex. 1014, 1, 4, 5; Ex. 1002 ¶¶ 32, 41, 78.

With respect to (B) and (D), the Specification admits that "[i]dentifying patients with pre-existing LVD is known to those skilled in the medicinal arts." Ex. 1001, 5:15–19. Petitioner further argues that Bernasconi 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. *See* Pet. 36–37; Ex. 1004, 8.

Claims 18 and 19 recite substantially the same steps as claim 17, except that iNO treatment in claim 18 is affirmatively provided only to the patient *not* having LVD. To the extent the prior art teaches the identification of patients with LVD, it correspondingly teaches the identification of those without the condition. In this

respect, Petitioner's declarant asserts that, because INOmax label does not draw a distinction between neonates with and without LVD, it thus discloses treating neonates having hypoxic respiratory failure with 20 ppm iNO, irrespective of whether they have, or do not have, LVD (steps (E) and (C), respectively). *See* Ex. 1002 ¶ 32 (citing Ex. 1014, 4).

For the reasons set forth above, we are persuaded, based on the current record, that Petitioner has shown a reasonable likelihood that it would prevail on its assertion that claims 17–19 are unpatentable over the cited art.

8. Claims 2, 5, 6, 8, 13, and 15

Dependent claims 2, 5, 6, 8, 13, and 15 require that "the information of (i) and the information of (ii) [from the respective base claim] appear in prescribing information supplied to the medical provider with the cylinder containing compressed nitric oxide gas." As noted above, we accord no patentable weight to the method by which the information of (i) and (ii) are provided. In addition, Petitioner argues that INOmax label itself comprises "prescribing information" containing the information of (i) supplied to medical providers with NO gas cylinders, whereas "the combination of *Bernasconi* with *INOMAX label, Loh*, and *Goyal*, discloses providing the 'information of (ii)' as recited in the independent claims." Pet. 26–27.

For the above reasons, on the present record, we find that Petitioner has shown a reasonable likelihood that it would prevail on its assertion that claims 2, 5, 6, 8, 13, and 15 are unpatentable over the cited prior art.

C. Remaining Ground of Unpatentabilty

Petitioner also contends that claims 1–19 are unpatentable under 35 U.S.C. § 103(a) over the combination of Ichinose, INOmax label, Loh, Neonatal Group,

and Goyal. Pet. 42–59. Based on our institution of trial as to claims 1–19 as unpatentable under 35 U.S.C. § 103(a) over the combination of Bernasconi, INOmax label, Loh, and Goyal, we exercise our discretion not to institute a review of the additional asserted ground for reasons of administrative efficiency to ensure timely completion of the instituted proceeding. *See* 37 C.F.R. § 42.108(a); 35 U.S.C. § 314(a).

III. CONCLUSION

For the foregoing reasons, we find that the information presented in the Petition, in conjunction with Patent Owner's admission that it is known in the art to identify patients with pre-existing LVD, establishes a reasonable likelihood that Petitioner would prevail in showing that claims 1, 7, 12, and 14 are unpatentable for anticipation under 35 U.S.C. § 102(a) and/or obviousness under 35 U.S.C. § 103(a). On the present record, we further find a reasonable likelihood that Petitioner would prevail in showing that claims 1–19 are unpatentable under 35 U.S.C. § 103(a). This is not a final decision as to the construction of any claim term or the patentability of claims 1–19. Our final decision will be based on the full record developed during trial.

IV. ORDER

For the reasons given, it is

ORDERED that *inter partes* review is instituted with regard to the following grounds:

Claims 1, 7, 12, and 14 of the '112 patent under 35 U.S.C. § 102(a) as anticipated by INOmax label;

Claims 1, 7, 12, and 14 of the '112 patent under 35 U.S.C. § 103(a) as obvious in view of INOmax label;

Claims 1–19 of the '112 patent under 35 U.S.C. § 103(a) as obvious over the combination of Bernasconi, INOmax label, Loh, and Goyal.

FURTHER ORDERED that pursuant to 35 U.S.C. § 314(a), *inter partes* review of the '112 patent is hereby instituted commencing on the entry date of this Order, and pursuant to 35 U.S.C. § 314(c) and 37 C.F.R. § 42.4, notice is hereby given of the institution of a trial.

FURTHER ORDERED that the trial is limited to the grounds listed in the Order. No other grounds are authorized.

PETITIONER:

Sanjay K. Murthy
sanjay.murthy@klgates.com

Sara Kerrane
Sara.kerrane@klgates.com

Margaux Nair
margaux.nair@klgates.com

Maria Doukas
maria.doukas@klgates.com

PATENT OWNER:

Dominick A. Conde
dconde@fchs.com

Raymond R. Mandra
rmandra@fchs.com