IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

INO THERAPEUTICS LLC and IKARIA, INC.,	)	
Plaintiffs,	)	
v.	)	C.A. No. 15-170 (GMS)
PRAXAIR DISTRIBUTION, INC. and PRAXAIR, INC.,	)	
Defendants.	)	

PLAINTIFFS' OPPOSITION TO DEFENDANTS' MOTION FOR JUDGMENT ON THE PLEADINGS FOR COUNTS I-V OF PLAINTIFFS' COMPLAINT

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I. NATURE AND STAGE OF PROCEEDINGS

On February 19, 2015, Plaintiffs INO Therapeutics LLC and Ikaria, Inc. (collectively "Plaintiffs") filed this suit alleging infringement of ten patents.[1] On December 8, 2015, Defendants Praxair Distribution, Inc. and Praxair, Inc. (collectively "Defendants") filed a motion pursuant to FEDERAL RULE OF CIVIL PROCEDURE 12(c) for judgment on the pleadings alleging that five asserted patents (a total of 147 claims) are ineligible under 35 U.S.C. § 101. (D.I. 36.)

II. SUMMARY OF ARGUMENT

1. Defendants have not even attempted to carry their heavy burden to show that the claims of the challenged patents are invalid under § 101 by clear and convincing evidence at this early stage of the litigation. Under the Supreme Court's two-step framework laid out in *Mayo Collaborative Services v. Prometheus Laboratories, Inc*., 132 S. Ct. 1289 (2012) and *Alice Corp. Pty. Ltd. v. CLS Bank International*, 134 S. Ct. 2347 (2014), Defendants must prove both that (a) the claims are directed to a natural law and (b) the series of claimed steps, as a whole, comprises conventional activity previously practiced in the field. Defendants did not submit any evidence in support of either proposition, a failure of proof that alone requires that this Court deny Defendants' motion for judgment on the pleadings, just as it did in *Vanda Pharmaceuticals Inc. v. Roxane Laboratories, Inc.*, Nos. 13-1973 & 14-757, D.I. 126, at 60:5-61:9, 62:14-16, 63:7-8 (D. Del. Sept. 2, 2015) (attached as Ex. A).[2]

2. At step one of the *Mayo*/*Alice* analysis, the parties dispute whether the claims are directed to a "natural law" at all. Defendants assert (without citing any evidence) that the challenged claims are allegedly directed to the "natural law" that "administration of nitric oxide

[1] On January 25, 2016, the parties filed a Joint Stipulation adding Plaintiff Mallinckrodt Hospital Products IP Ltd. as a plaintiff. (D.I. 50).

[2] Exhibits A-V are attached to this opposition brief. Exhibits 1-11 are attached to the Declaration of Dr. Rosenthal (Ex. B).

to children with a condition known as left ventricular dysfunction ('LVD') can cause pulmonary edema." (D.I. 36 at 1.) But Plaintiffs point to unrebutted evidence showing that there is no such "natural law" in any relevant sense under controlling precedent. At a minimum, that issue presents a factual dispute that precludes granting Defendants' premature motion.

3. Regardless, at step two of the *Mayo*/*Alice* analysis, the parties also dispute whether, in addition to the purported natural law, the claims recite only a series of conventional steps that were routinely performed prior to the inventions described and claimed in the challenged patents. Defendants make such an assertion, but all of the evidence—the patent specification, prosecution history, and extrinsic evidence (including the lone piece of evidence that Defendants did submit)—demonstrates that, far from being conventional, the combination of steps was contrary to the well-established scientific view at the time. The claimed inventions are precisely of the type that *Mayo* itself and other cases have repeatedly made clear remain patent eligible: modified uses of an existing drug. But, at a minimum, that is yet another factual issue that precludes granting Defendants' premature motion.

III. STATEMENT OF FACTS

A. The Five Challenged Patents

Defendants' motion challenges five of the patents Plaintiffs assert in this action: U.S. Patent Nos. 8,282,966 ("the '966 patent"), 8,293,284 ("the '284 patent"), 8,431,163 ("the '163 patent"), 8,795,741 ("the '741 patent"), and 8,846,112 ("the '112 patent") (collectively the "challenged patents"). The dates of issuance for the challenged patents range from October 9, 2012, to September 30, 2014—all of which were after the Supreme Court's March 2012 decision in *Mayo* and two of which were after the Supreme Court's June 2014 decision in *Alice*.

The challenged patents share a common specification and generally recite (or relate to) new methods for safely treating critically ill infants who are candidates for inhaled nitric oxide

("iNO") treatment while reducing the risk that the treatment will result in pulmonary edema and other serious adverse events ("SAEs").[3] Specifically, the patents disclose a solution to the previously unknown problem that pediatric patients suffering from hypoxic respiratory failure who also suffer from left ventricular dysfunction ("LVD") have a greater risk of SAEs if they are administered iNO. (*See, e.g.*, Ex. 1, '966 patent at 13:16-14:3.)[4]

The challenged patents have a total of 147 claims. For example, claim 1 of the '966 patent provides:

> 1. A method of reducing the risk of occurrence of pulmonary edema associated with a medical treatment comprising inhalation of 20 ppm nitric oxide gas, said method comprising::
>
> (a) performing echocardiography to identify a child in need of 20 ppm inhaled nitric oxide treatment for pulmonary hypertension, wherein the child is not dependent on right-to-left shunting of blood;
>
> (b) determining that the child identified in (a) has a pulmonary capillary wedge pressure greater than or equal to 20 mm Hg and thus has left ventricular dysfunction, so is at particular risk of pulmonary edema upon treatment with inhaled nitric oxide; and
>
> (c) excluding the child from inhaled nitric oxide treatment based on the determination that the child has left ventricular dysfunction and so is at particular risk of pulmonary edema upon treatment with inhaled nitric oxide.

B. Background of the Invention

The inventions disclosed in the challenged patents arose from observations made during the INOT22 clinical study (Example 1 in the specification) which involved administering INOmax® (Plaintiffs' iNO product) to pediatric patients. (Ex. 1, '966 patent at 9:20-14:3.) Designed by the leading experts in the field and consistent with the state of the art at the time, the INOT22 study did not exclude patients with pre-existing LVD. (*Id.* at 9:20-64.) Only after

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[3] The '112 patent recites methods of providing "pharmaceutically acceptable gas" to those who will safely treat critically ill infants who are candidates for iNO treatment along with information designed to reduce the risk that the treatment will result in pulmonary edema and other SAEs.

[4] For convenience, citations are to the '966 patent specification unless otherwise noted.

significant numbers of SAEs occurred did it become clear that administering iNO to patients with LVD could be risky, leading to the claimed methods for safely providing iNO to pediatric patients, including term and near-term infants (known as "neonates"). (*Id*. at 9:20-14:3.)

1. The Prior Use of iNO in Neonates Suffering From Hypoxic Respiratory Failure Only Excluded Neonates Dependent on Right-to-Left Shunting, Not Those With Preexisting LVD

Plaintiffs' INOmax® product is FDA-approved for administration by inhalation to neonates suffering from hypoxic respiratory failure (abnormally low levels of oxygen in the bloodstream) associated with clinical or echocardiographic evidence of pulmonary hypertension (high pressure in the blood vessels going to the lungs), known as persistent pulmonary hypertension of the newborn ("PPHN"). (Ex. B, Rosenthal Decl. at ¶ 6; Ex. 8, Current INOmax® Label.) In such neonates, the pulmonary vessels fail to adequately relax, and there is insufficient gas exchange. (Ex. B, Rosenthal Decl. at ¶ 6.) iNO relaxes the small vessels that are in close proximity to the aerated parts of the lung, increasing blood flow to the lungs. (*Id*.)

However, administering iNO has significant risks. (*Id*. ¶ 7.) Some neonates have a severe congenital heart disease that prevents the left side of the heart from pumping blood to the rest of the body. (*Id*.) For these neonates, pulmonary vasoconstriction (normally problematic as discussed above) is actually *beneficial* (indeed, life-saving) because it creates a right-to-left shunt that allows the right ventricle to take on the role of the nonfunctioning left ventricle by pumping adequately oxygenated blood directly to the systemic circulation. (*Id*.) These neonates are described as being *dependent* upon right-to-left shunting of blood ("RTL-Dependent"). Administering iNO to such a neonate (lowering pulmonary vascular resistance) reduces blood flow to the body and coronary arteries and puts the infant at high risk of, among other things, severe acidosis, cardiogenic shock, and sudden death. (*Id*.) For these reasons, when the FDA

first approved INOmax® as safe and effective, it was contraindicated for RTL-Dependent neonates. (*Id.*; Ex. 2, 2000 INOmax® Label.)

INOmax® was not contraindicated for any other class of neonates including those *with* LVD, but who were *not* RTL-Dependent ("non-RTL-Dependent"). This was consistent with the prior clinical studies submitted in support of the original FDA approval of INOmax® that administered iNO to pediatric patients, including neonates, which did exclude non-RTL-Dependent neonates suffering from LVD. (Ex. B, Rosenthal Decl. at ¶ 8; Ex. 3; Ex. 4.)

2. The Original INOT22 Study Protocol Did Not Exclude Neonates with Non-RTL-Dependent LVD

Beginning in 2004, Plaintiff INO Therapeutics LLC ("INOT") sponsored a clinical trial (the "INOT22 Study") that compared the use and side effects of oxygen, iNO, and a combination of oxygen and iNO for determining pulmonary reactivity. (Ex. 1, '966 patent at 9:65-67.) The INOT22 Protocol did not exclude pediatric patients with other types of pre-existing LVD. (*Id.* at 9:43-55; Ex. B, Rosenthal Decl. at ¶ 9; Ex. 5 at ¶¶ 9, 11; Ex. 6 at ¶ 7.) The INOT22 study was designed by INOT and a committee of "internationally recognized experts" in pediatric heart and lung disease ("the INOT22 Steering Committee"). (Ex. B, Rosenthal Decl. at ¶ 9; Ex. 5 at ¶¶ 7-8; Ex. 6 at ¶ 8.) Before the study began, the INOT22 protocol was carefully reviewed by more than 115 individuals "experienced in and responsible for the review of clinical trial protocols for patient safety"—including institutional review boards, independent ethics committees, the U.S. Food & Drug Administration ("FDA"), and equivalent agencies in other countries. (Ex, B, Rosenthal Decl. at ¶ 9; Ex. 6 at ¶ 11.) *Not one* suggested that iNO might increase the likelihood of adverse events in pediatric patients with non-RTL-Dependent LVD. (*Id.*)

3. Unanticipated SAEs Occurred During the INOT22 Study, the Study Was Amended, and the Rate of SAEs Was Significantly Reduced

Despite the review by these renowned experts in the field, five SAEs were observed in the first 24 subjects enrolled in the INOT22 study, a rate much higher than the INOT22 Steering Committee and INOT expected. (Ex. 1, '966 patent at 12:30-13:5; Ex. B, Rosenthal Decl. at ¶ 10; Ex. 5 at ¶ 12.) The SAEs were cardiovascular events, including pulmonary edema (accumulation of fluid in the lungs), cardiac arrest and hypotension (low blood pressure); one child who developed pulmonary edema died. (Ex. 1, '966 patent at 12:30-13:5) Some of the "patients suffering [SAEs] had severe [LVD] . . . and exhibited during their right-sided cardiac catheterizations an increased pulmonary capillary wedge pressure ('PCWP') of greater than 20 mm Hg, indicative of elevated pressures in the upper chamber of the left side of the heart (the left atrium)." (Ex. C at ¶ 21.) From these results, the inventors determined that "pediatric patients with left ventricular dysfunction" could be at "an increased risk of adverse events when inhaled NO was administered." (Ex. D at ¶ 11; Ex. B, Rosenthal Decl. ¶ 11.)

After these unexpected SAEs, the INOT22 study protocol was amended to exclude patients with pre-existing non-RTL-Dependent LVD, *i.e.*, those having a PCWP greater than 20 mm Hg. (Ex. 1, '966 patent at 12:24-38; Ex. B, Rosenthal Decl. at ¶ 12; Ex. 5 at 13.) Thereafter, "the rate of [SAEs] (including [SAEs] associated with heart failure) was significantly reduced." (Ex. 5 at ¶ 14; Ex. B, Rosenthal Decl. at ¶ 12.) While five SAEs were reported in the first 24 patients of the study, only two SAEs were reported in the 100 patients after the protocol was amended. (Ex. 5 at ¶ 14; Ex. B, Rosenthal Decl. at ¶ 12.) On August 28, 2009, at INOT's request, the FDA approved a change to the INOmax® label to provide a warning that the use of iNO in patients with pre-existing LVD could cause SAEs, such as pulmonary edema. (Ex. 5 at ¶¶ 15-16; Ex. 2, 2000 Label; Ex. 8, Current Label; Ex. B, Rosenthal Decl. at ¶ 15.)

Dr. David Wessel, chair of the INOT22 Steering Committee, stated that "[a]t the time of the design of the INOT22 Study protocol, neither [he], the other Steering Committee members, nor the study Sponsor appreciated or anticipated that a child with left ventricular dysfunction who is not dependent on right-to-left shunting of blood would be at additional risk when treated with [iNO]. This is the reason such children were not originally excluded from the INOT22 Study entry criteria." (Ex. 7 at ¶ 6.) Had the adverse events been obvious, Dr. Wessel would have had to have "act[ed] either negligently or intentionally to harm babies, and [he] most certainly [did] not." (*Id.* at ¶ 8.) The same applies to the "at least 115 individuals experienced in and responsible for the review of clinical trial protocols for patient safety," as well as the FDA and European Health Authorities that reviewed the original INOT22 protocol. (Ex. 6, ¶ 11.) None raised a concern about increased risk of using iNO in children with LVD who were non-RTL-Dependent. (*Id.*; Ex. B, Rosenthal Decl. at ¶ 9.) As inventor Dr. Baldassarre stated, prior to the INOT22 Study, it defied "common sense to any expert in this field" to not utilize iNO with this patient population. (Ex. 5 at ¶ 11.)

C. Prosecution History

On June 30, 2009, based on the surprising results of the INOT22 study showing that safe use of iNO could warrant excluding neonates with non-RTL-Dependent LVD, INOT filed U.S. Patent Application No. 12/494,598, which ultimately issued as the five challenged patents.

Throughout the prosecution history, and in particular after the Supreme Court's decision in *Mayo*, the examiner thoroughly considered the patent-eligibility of the claims under § 101, in consultation with the U.S. Patent and Trademark Office's ("PTO") § 101 specialists and supervisors. (*See, e.g.*, Ex. E at INO_19251, Ex. F. at INO_19441, Ex. G at INO_20242 ('112 patent file history excerpts).) Post-*Mayo*, with further input and direction from the PTO, the applicant amended certain claims specifically to avoid any possible § 101 problems and to

overcome §101 rejections. (*See* Ex. H at INO_11813, Ex. I at INO_11829 ('966 patent file history excerpts); Ex. J at INO_15323 ('284 patent file history excerpt); Ex. K at INO_19816, Ex. L at INO_20196 ('112 patent file history excerpts).)

IV. LEGAL STANDARDS

A. Rule 12(c) Motions

On a motion for judgment on the pleadings, "the court 'accept[s] all factual allegations as true, construe[s] the complaint in the light most favorable to the plaintiff, and determine[s] whether, under any reasonable reading of the complaint, the plaintiff may be entitled to relief.'" *Money Suite Co. v. 21st Century Ins. & Fin. Servs., Inc.*, C.A. No. 1:13-cv-984-GMS, 2015 WL 436160, at *1 (D. Del. Jan. 27, 2015) (citation omitted).

Patent-eligibility under § 101 "is a question of law based on underlying facts," as this Court recently recognized. Ex. U, *Vanda Pharm. v. Roxane Labs., Inc.*, Nos. 1:13-cv-1973 & 1:14-cv-757, D.I. 148, at 1 n.1 (D. Del. Dec. 30, 2015) (material issues of fact precluded finding certain medical treatment method claims ineligible under §101) (citing *In re Cominsky*, 554 F.3d 967, 975 (Fed. Cir. 2009)); *see also Versata Dev. Grp., Inc. v. SAP Am., Inc.*, 793 F.3d 1306, 1334, 1336 (Fed. Cir. 2015) (upholding trial forum's "underlying fact findings and credibility determinations" regarding what constitutes conventional activity for § 101 analysis); *Accenture Glob. Servs. Gmbh v. Guidewire Software, Inc.*, 728 F.3d 1336, 1341 (Fed. Cir. 2013) (§ 101 eligibility is legal issue that "may contain underlying factual issues") (citation omitted). And this Court has explained that a patent claim will not be found directed towards patent-ineligible subject matter at the pleading stage unless, under "'the *only* plausible reading of the patent[,] … there is clear and convincing evidence of ineligibility.'" *Money Suite Co.*, 2015 WL 436160, at *2 (citation omitted).

B. Section 101

Section 101 of the Patent Act provides that "[w]hoever 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." 35 U.S.C. § 101. Such patent-eligible subject matter "includes a new use of a known process, machine, manufacture, composition of matter, or material." 35 U.S.C. § 100(b).

These broad classifications are limited by three exceptions. "Laws of nature, natural phenomena, and abstract ideas are not patentable." *Alice*, 134 S. Ct. at 2354 (quoting *Ass'n for Molecular Pathology v. Myriad Genetics, Inc.*, 133 S. Ct. 2107, 2116 (2013)). But the Supreme Court has eschewed bright line rules in applying these exceptions, cautioning that courts must "tread carefully in construing this exclusionary principle lest it swallow all of patent law" because "[a]t some level, 'all inventions . . . embody, use, reflect, rest upon, or apply laws of nature, natural phenomena, or abstract ideas.'" *Alice*, 134 S. Ct. at 2354 (quoting *Mayo*, 132 S. Ct. at 1293.)); *see also*, *e.g.*, *Money Suite Co.*, 2015 WL 436160, at *2 (quoting same).

In *Mayo* and *Alice*, the Supreme Court provided a two-part framework for determining patent eligibility under § 101. *Mayo*, 132 S. Ct. at 1294, 1296-98; *Alice*, 134 S. Ct. at 2355, 2360. First, this Court "determine[s] whether the claims at issue are directed to one of those patent-ineligible concepts." *Alice*, 134 S. Ct. at 2355 (citation omitted). Second, if so, the Court determines whether the claims are nonetheless eligible because they include something more—often called an "inventive concept." *Id.* In assessing whether the claims are inventive, the Court "consider[s] the elements of each claim both individually and as an ordered combination to determine whether the additional elements transform the nature of the claim into a patent-eligible application." *Id.* (internal quotations and citation omitted). Claims are eligible if, "as a whole," they recite more than "well-understood, routine, conventional activity previously engaged in by

scientists who work in the field." *Mayo*, 132 S. Ct. at 1298. Such claims do not "risk disproportionately tying up the use of the underlying ideas . . . and therefore remain eligible for the monopoly granted under our patent laws." *Alice*, 134 S. Ct. at 2354-55 (citation omitted).

Notably, in *Mayo*, the Supreme Court emphasized two points critical to this motion. First, the Court noted that:

> here, as we have said, the steps add nothing of significance to the natural laws themselves. Unlike, say, a typical patent on a new drug *or a new way of using an existing drug*, the patent claims do not confine their reach to particular applications of those laws.

132 S. Ct. at 1302 (emphasis added). Thus, the Supreme Court reiterated that "a typical patent on … a new way of using an existing drug" *is* patent-eligible because even if it implicates a natural law, its "reach" is "confined" to "particular applications" of such a law. *Id.* Second, the Court also distinguished and reaffirmed its holding in *Diamond v. Diehr*, 450 U.S. 175, 185 (1981), where the Court found that claims on an improved method of curing rubber using a known equation were patent eligible because "the *combination* of . . . steps" were not "in context obvious, already in use, or purely conventional." *Mayo*, 132 S. Ct. at 1299 (emphasis added).

Similarly, in *Myriad*, the Supreme Court emphasized that "'the first party with knowledge of [a law of nature] is in an excellent position to claim applications of that knowledge'" in the form of medical methods. 133 S. Ct. at 2120 (quoting *Ass'n For Molecular Pathology v. U.S. PTO("Myriad")*, 689 F.3d 1303, 1349 (Fed. Cir. 2012) (Bryson, J., concurring and dissenting)). The Court pointed to one such patent-eligible method for detecting a certain alteration in a certain gene. *See id*. (agreeing with *Myriad*, 689 F.3d at 1349 (Bryson, J.) (citing U.S. Patent No. 5,743,441, claim 21)). Also in *Myriad*, the Federal Circuit found eligible a method of screening potential cancer therapeutics by growing host cells in the presence of and in the absence of a compound and comparing the growth rate, "wherein a slower rate of growth . . .

in the presence of said compound is indicative of a cancer therapeutic." 689 F.3d at 1310, 1335-37. The court held that the claim "does not simply apply a law of nature" but instead "applies certain steps to transformed cells that . . . are a product of man, not of nature." *Id.* at 1336. The Supreme Court declined to review that holding.

Further, the Supreme Court and Federal Circuit have recognized that the § 101 inquiry and the prior art inquiries of §§ 102 (novelty) and 103 (non-obviousness) "might sometimes overlap," *Mayo*, 132 S. Ct. at 1304, and that "pragmatic analysis of §101 is facilitated by considerations analogous to those of §§ 102 and 103 as applied to the particular case," *Internet Patents Corp. v. Active Network, Inc.*, 790 F.3d 1343, 1347 (Fed. Cir. 2015). In that vein, in a § 103 case, the Federal Circuit recently acknowledged that identifying a group of patients who should not receive conventional treatment can qualify as a new way of using an existing drug:

> [I]n the field of personalized medicine, … a particular treatment may be effective with respect to one subset of patients *and ineffective (and even harmful) to another subset of patients.* Singling out a *particular subset of patients* for treatment (for example, patients with a particular gene) *may reflect a new and useful invention that is patent eligible* despite the existence of prior art or a prior art patent disclosing the treatment method to patients generally.

Prometheus Labs., Inc. v. Roxane Labs., Inc., 805 F.3d 1092, 1098 (Fed. Cir. 2015) (citation omitted; emphasis added).

V. ARGUMENT

Defendants' motion for judgment on the pleadings of invalidity under § 101 should be denied because: (a) Defendants have a high burden to show invalidity of the challenged patents by clear and convincing evidence and have not even attempted to meet that burden by submitting evidence on any of the disputed factual issues, (b) the claims are not directed to an inviolable natural law (or there is at least a factual dispute on that score), and (c) even if they were directed

to such a natural law, the claims do not merely recite conventional activity (or that, too, raises a factual dispute).

A. Defendants' Motion Should Be Denied Because They Have Failed To Submit Evidence Required To Satisfy Their High Burden

This Court should deny Defendants' motion because they have not come close to meeting their high burden to show that all 147 issued claims of the five challenged patents are invalid. To succeed on their motion for judgment on the pleadings, Defendants must demonstrate by clear and convincing evidence that the claims do nothing more than embody a law of nature and add routine and conventional steps—and Defendants must make a showing so indisputable that no reasonable trier of fact could conclude otherwise. *See, e.g.*, *Money Suite Co.*, 2015 WL 436160, at *1-2.

In the face of this substantial burden, Defendants failed to submit any evidence to show either: (1) the issued claims are directed to a law of nature or (2) the issued claims, as a whole, recite only conventional activity. Defendants simply *assert* that both are true. (D.I. 36 at 8). But that *ipse dixit* attorney argument is not evidence—and does not warrant disposing of this case at this stage, on the pleadings. This Court should deny Defendants' motion for this reason alone.[5]

This Court recently confronted the same issue in *Vanda Pharmaceuticals Inc. v. Roxane Laboratories, Inc.*, Nos. 13-1973 & 14-757. In that case, the defendant moved to dismiss the

[5] At one point, for example, Defendants point to a passage from the '966 patent specification (D.I. 36 at 8), but that passage hardly constitutes clear and convincing evidence that the claims recite nothing more than a law of nature. Instead, the passage notes that "[d]uring, 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" and that "a precaution for patients with LVD was proposed to be included in amended prescribing information for lNOmax®." (Ex. 1, '966 Patent at 9:31-40.)

suit, arguing that the asserted medical treatment method claims were invalid under § 101. This Court denied the motion to dismiss and declined to resolve the § 101 issue at the pleading stage without an evidentiary record. (Ex. U, *Vanda Pharm.*, D.I. 126, at 60:5-61:9, 62:14-16, 63:7-8 (D. Del. Sept. 2, 2015).) This Court should do likewise here.[6]

B. Defendants' Motion Should Be Denied Because The Parties Dispute That The Claims Recite a "Law Of Nature"

At step one of the *Mayo*/*Alice* analysis, Defendants argue that there is allegedly an inviolable "law of nature" that "administration of nitric oxide to children with a condition known as left ventricular dysfunction ('LVD') can cause pulmonary edema." (D.I. 36 at 1.) That argument fails for two independent reasons.

First, it is at best a disputed fact issue whether the subject claims are directed to a natural law. Plaintiffs have submitted evidence that the discovery underlying the asserted patent claims are not predicated on a natural law. (Ex. B, Rosenthal Decl. ¶¶ 16-26.) For example, Dr. Rosenthal testifies that: (i) the interactions between the drug (iNO) and a child's circulatory and respiratory systems are complex and not fully understood, (ii) even if, in the aggregate, the patient population (or even the child patient population) as a whole exhibits a higher rate of adverse events, that does not mean not *each and every* child with LVD is *necessarily* at increased risk of a set of adverse events (let alone any particular adverse event, such as pulmonary edema) when treated with nitric oxide, and (iii) in some circumstances, nitric oxide could itself be effective and appropriate for treating a child's LVD. (*Id.*)

Defendants submit no evidence to the contrary and instead cite only the patents themselves. (D.I. 36 at 8 (citing '966 patent at 9:22-40).) The patents, however, do not support

[6] The two cases upon which Praxair most heavily relies, *Mayo* and *Ariosa*, were decided on summary judgment, after factual development, not on the pleadings. *See Mayo*, 132 S. Ct. at 1296; *Ariosa Diagnostics, Inc. v. Sequenom, Inc.*, 788 F.3d 1371, 1375 (Fed. Cir. 2015).

Defendants' assertion of a "natural law." To the contrary, the shared specification states that administering iNO "*may* be detrimental to patients with . . . LVD" (Ex. 1, '966 patent at 9:34-35) (emphasis added) and that "patients who had pre-existing LVD *may* experience an increased rate of [adverse events, such as pulmonary edema]" (*id.* at 13:62-63) (emphasis added), but (because a "law of nature" is *not* at issue here) they also note that "[t]he benefit/risk of using iNO in patients with clinically significant LVD should be evaluated on a case by case basis" (*id.* at 13:66-14:1). (*See also* Ex. M, '966 file history excerpt at INO_8910 (claims provide for "mandatory exclusion . . . even though the [iNO] treatment would be potentially beneficial to the patient").) Defendants' motion fails at this stage because Defendants have not remotely carried their burden to show that the asserted claims are predicated on an inviolate law of nature and because the available evidence thus far shows that they do not. At a minimum, this presents a disputed fact issue not suitable for resolution at the pleading stage.

Second, Defendants' assertion conflicts with established law. Thus, if Defendants' purported principle is a patent-ineligible "natural law," then *any* use of an existing drug in a certain way to obtain a desired outcome is likewise a patent-ineligible "natural law" and no patent can issue on a new method for using a drug. But the Supreme Court expressly rejected that sweeping position in *Mayo*, cautioning that at some level "all inventions . . . embody, use, reflect, rest upon, or apply laws of nature" but that "a typical patent on . . . a new way of using an existing drug" remains patent-eligible. 132 S. Ct. at 1293, 1302. The Supreme Court also rejected a similar argument in *Myriad* in finding patent eligible claims on human-modified DNA. 133 S. Ct. at 2119. The party challenging eligibility argued that "'[t]he nucleotide sequence of cDNA is dictated by nature, not by the lab technician,'" but the Court determined that, while "[t]hat may be so," it does not make it a "product of nature" for purposes of the § 101 analysis.

Id. Indeed, Defendants' expansive approach to "natural" phenomena would render ineligible any man-made compositions that achieve useful results through "natural" processes, contrary to decades of case law. *See, e.g.*, *Diamond v. Chakrabarty*, 447 U.S. 303, 305, 309-10 (1980) (finding patent eligible claims on human-modified bacterium that could "break[] down multiple components of crude oil").[7]

Defendants' have failed to demonstrate that the challenged claims are directed to a law of nature at step one of the *Mayo*/*Alice* analysis—at most, Defendants has raised a disputed fact issue. Their pleading-stage motion should, therefore, be denied.

C. Defendants' Motion Should Be Denied Because The Parties Dispute Whether The Claims "As A Whole" Recite Only Conventional Activity

Even if Plaintiffs' challenged patent claims were directed to a natural law, they would nonetheless be eligible at step two of the *Mayo*/*Alice* analysis because, as a whole, the claims describe an application of that purported law—they do not just recite a conventional series of steps previously engaged in by scientists who work in the field. *See Mayo*, 132 S. Ct. at 1298.

For example, claim 1 of the '966 patent recites (1) identifying a child in need of iNO treatment (one who is not RTL-dependent), (2) determining that the child has LVD, and (3) excluding that child from iNO treatment to lessen the risk of pulmonary edema. (*Supra* at § III.A.) Other claims provide for assessing patients with ongoing iNO treatment and discontinuing such treatment, as necessary, to avoid the risk of pulmonary edema or other serious adverse events. (*See, e.g.*, Ex. V, '741 patent cl. 9, 17.) Defendants argue that such claim

[7] Praxair's reliance on *Ariosa* and *Endo* is unavailing as it was essentially undisputed that the claims in those cases were directed to natural laws or natural phenomena. *See Ariosa*, 788 F.3d at 1376 (explaining that it was "undisputed" that the DNA being detected in maternal blood was naturally occurring and the finding claims were "directed to detecting the presence of" that "naturally occurring thing"); *Endo Pharm., Inc. v. Actavis Inc.*, Civil Action No. 14-1381-RGA, 2015 WL 5580488, at *6 (D. Del. Sept. 23, 2015) (patentee "effectively concede[d] the first step of the *Mayo* analysis"), *adopted by* 2015 WL 7253674 (D. Del. Nov. 17, 2015).

elements in "combination" were conventional—*i.e.*, that it was well-understood and routine that children with LVD, but who are not RTL-dependent, should be excluded from treatment with iNO. (*E.g.*, D.I. 36 at 6, 9-12, 18.) But Defendants submit no evidence that each claim, as a whole, constitutes conventional activity in the field and the only evidence submitted thus far shows the opposite: although the individual analytical techniques were well-known and practiced, the process described in the claims was unconventional and not appreciated in the art.

First, the specification explains that, prior to the patent, non-RTL-dependent children with LVD were not excluded from iNO treatment. (*Supra* at § III.B.1.) As discussed, the INOT22 study itself did not exclude such children, even though it was designed and reviewed by more than 115 medical professionals in the public and private sectors. (*Id.*) And *none* of those professionals suggested that iNO might increase the likelihood of adverse events in pediatric patients with non-RTL-Dependent LVD. (*Id.*) It is plain, therefore, from the face of the patent that such exclusions were far from "conventional" and "routine," as Defendants must show for their motion to succeed. *See Mayo*, 132 S. Ct. at 1298; *see also, e.g.*, *Ameritox, Ltd. v. Millennium Health, LLC*, 88 F. Supp. 3d 885, 907 (W.D. Wisc. 2015) ("if inventors engage in activities that run *counter* to scientific thought, those activities can hardly be considered conventional under § 101," such as "when a patent involves a combination of elements that the scientific community would not have thought to use").

Second, the patent file histories support that conclusion. In prosecuting the patents, the examiners thoroughly vetted the claims under § 101, consulted with the PTO's in-house experts on § 101, and applied the holding in *Mayo* in finding the claims patent eligible. (*See supra* at § III.C.) Indeed, for one of the challenged patents, the claims were twice rejected in the wake of *Mayo* but, after extensive discussion between the applicant and the PTO (including the office's

§ 101 specialists), the applicant amended the claims and overcome the rejection. (*See id.*; Ex. N at INO_19193, Ex. O at INO_19429, Ex. P at INO_19469, Ex. Q at INO_19440-42, ('112 file history excerpts).)[8] The examiners also found, after much back and forth, that the claims were not obvious in light of prior art. (*See, e.g.*, Ex. R at INO_12144-46, Ex. S at INO_12154 ('966 file history excerpts).) The PTO's thorough consideration of the facts makes clear that there is nothing "conventional" about the claimed series of steps.

Third, more recently, the PTO's Patent Trial and Appeal Board ("PTAB") rejected Defendants' requests to institute *inter partes* review proceedings as to four of the challenged patents (the '966, '284, '163, and '741 patents). (Ex. T, July 29, 2015 Non-Institution Decision.) The PTAB held that Defendants failed to show that the claims of those patents were likely obvious in light of prior art. Of particular relevance here, the PTAB rejected Defendants' contention that it was well-understood in the art that "certain patients who have [LVD] would be at risk of pulmonary oedema, even if not dependent on right-to-left shunting of blood, and should not be treated with [iNO]." (*Id.* at 15.)[9]

Fourth, consistent with that overwhelming intrinsic evidence, Plaintiffs' expert, Dr. Rosenthal, testifies that it was unknown in the field that it might be necessary to exclude from treatment children that are not RTL-dependent but have LVD. (Ex. B, Rosenthal Decl. ¶¶ 9-14.) As Dr. Rosenthal explains, "[p]rior to the INOT22 study with the amended protocol, there was no convincing scientific evidence that demonstrated an association between use of

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[8] *See also* Ex. U, *Vanda Pharm. v. Roxane Labs., Inc.*, Nos. 1:13-cv-1973 & 1:14-cv-757, D.I. 148, at 1 n.1 (noting that "the PTO explicitly considered the . . . patent in light of *Mayo* and upheld the patentability" and denying summary judgment of invalidity under § 101).

[9] Praxair asserts that the PTAB's findings are irrelevant because they related to § 103 not § 101. (D.I. 36 at 1 n.1, 12 n.4.) Although those sections provide separate requirements, the analyses "sometimes overlap." *Mayo*, 132 S. Ct. at 1304; *see Internet Patents*, 790 F.3d at 1347 (§ 101 inquiry can be "facilitated by considerations analogous to those of . . . [§] 103"); *supra* at § IV.B.

nitric oxide in young infants with LVD and serious adverse events, such as pulmonary edema." (*Id.* ¶ 13.)

Similarly, the only piece of evidence that Defendants submit—the initial FDA-approved label for INOT's iNO product (Ex. 2, 2000 INOmax® Label)—further confirms that the claims were *not* merely conventional practices. Although the label stated that iNO was contraindicated for those with RTL-dependency, it tellingly did *not* warn against using iNO for those who were *not* RTL-dependent but had LVD. (*See id.*) Only *after* the INOT22 study surprised the medical community did INOT (with FDA approval) amend the label to indicate the potential risk for that particular subset of the patient population. (Ex. 8, Current INOmax® Label.) Therefore, the available extrinsic evidence, consistent with the patent specification and file history, shows that claimed steps absolutely do not recite "well-understood, routine, conventional activity previously engaged in by scientists who work in the field." *Mayo*, 132 S. Ct. at 1298.

Defendants rely heavily on *Mayo*'s holding that certain medical method claims are ineligible. (*E.g.*, D.I. 36 at 6-7, 11-12.) In *Mayo*, however, there was no dispute that those in the field "routinely" "engaged in" both of the claims' active steps in *combination* (administering the drugs and measuring the resulting metabolites) and that the claims did not require the doctor to "actually alter his treatment decision in the light of the test." 132 S. Ct. at 1296-98. In contrast, here, there is no evidence here that the recited steps were ever (let alone routinely) previously performed and the challenged claims *do* require an actual impact on the treatment of patients (either excluding or terminating patients from treatment). It is plain, therefore, that the claims here recite what was lacking in *Mayo*—"a new way of using an existing drug," which *Mayo* itself confirms is patent eligible. *Id.* at 1302. Indeed, "'[a]s the first party with knowledge of the [increased aggregate risk], [INO] was in an excellent position to [and did] claim [patent-eligible]

applications of that knowledge.'" *Myriad*, 133 S. Ct. at 2120 (citation omitted). In short, by reciting an "unconventional step[]," the asserted claims are thereby patent eligible (or at least a fact dispute exists on that score). *Mayo*, 132 S. Ct. at 1300.

Similarly, the Federal Circuit recently recognized that where a particular treatment is "ineffective (and even harmful)" to a "particular subset of patients," a treatment regime that excludes that subset "*may reflect a new and useful invention that is patent eligible* despite the existence of prior art or a prior art patent disclosing the treatment method to patients generally." *Prometheus Labs., Inc.*, 805 F.3d at 1098 (emphasis added); *see also Parks v. Booth*, 102 U.S. 96, 102 (1880) ("Modern inventions very often consist merely of a new combination of old elements or devices, where nothing is or can be claimed except the new combination."); *DDR Holdings, LLC v. Hotels.com, L.P.*, 773 F.3d 1245, 1258 n.5 (Fed. Cir. 2014) (same). That is precisely what the claims do here, based on all of the record evidence, even at this early stage.[10]

The challenged claims here are also like the ones in *Diehr*, 450 U.S. at 185. In that case, the Supreme Court found eligible claims for an improved process for curing rubber because, although the steps were individually conventional activity in the industry and added only a "well-known" mathematical equation, *id.* at 187, "the *combination* of . . . steps" were not "in context obvious, already in use, or purely conventional." *Mayo*, 132 S. Ct. at 1299 (emphasis added). As a whole, the claims "solve[d] a technological problem in 'conventional industry practice.'" *Alice*, 134 S. Ct. at 2358 (quoting *Diehr*, 450 U.S. at 178). So too here.

In the end, the Defendants' argument devolves into the suggestion that the "excluding" type steps recited in the asserted claims are "not transformative." (D.I. 36 at 11.) Defendants'

[10] In contrast, in *Endo*, it was undisputed that the relevant patient group was well-understood: the patent at issue "recognize[d] the use of oxymorphone for pain relief is a well-understood activity." 2015 WL 5580488, at *8.

argument ignores that the salient inquiry is whether the ordered *combination* of steps is sufficient to ensure that the claims do more than patent the natural law itself. Here, those combined steps plainly do; based on the evidence of record, Defendants have failed to show that the "combination of those steps, were in context obvious, already in use, or purely conventional." *Mayo*, 132 S. Ct. at 1299. Indeed, the evidence—including the specification itself—shows that the steps were non-obvious, not in use, and unconventional. (*See* Ex. 1, '966 patent at 9:7-10 ("An analysis of AEs and SAEs from both the ClNRGl 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."); *id.* at 12:25-26 ("In INOT22, a baseline PCWP value was not included as exclusion criteria"); *id.* at 12:27-34 ("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").)

In sum, and viewing all of the facts in the light most favorable to Plaintiffs, the claims "as an ordered combination" are the opposite of "purely conventional" activity; they instead constitute an inventive application of the (purported) natural law under cases like *Mayo*, *Myriad*, *Prometheus*, and *Diehr*. At worst, there is a disputed fact issue that cannot be resolved on the pleadings and precludes granting Defendants' motion.

VI. CONCLUSION

For the foregoing reasons, this Court should deny Defendants' motion for judgment on the pleadings because the challenged patent claims satisfy 35 U.S.C. § 101 or, at a minimum, there are disputed fact issues not suitable for resolution at the pleading stage.

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January 27, 2016

CERTIFICATE OF SERVICE

I hereby certify that on January 27, 2016, I caused the foregoing to be electronically filed with the Clerk of the Court using CM/ECF, which will send notification of such filing to all registered participants.

I further certify that I caused copies of the foregoing document to be served on January 27, 2016, upon the following in the manner indicated:

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EXHIBIT A

IN THE UNITED STATES DISTRICT COURT

IN AND FOR THE DISTRICT OF DELAWARE

- - -

VANDA PHARMACEUTICALS INC.,	)	Civil Action
	)	
Plaintiff,	)	
	)	
v.	)	
	)	
ROXANE LABORATORIES, INC.,	)	
	)	
Defendant.	)	No. 14-757-GMS

- - -

Wilmington, Delaware
Wednesday, September 2, 2015
2:00 p.m.
Markman Hearing

- - -

BEFORE: HONORABLE GREGORY M. SLEET, U.S.D.C.J.

APPEARANCES:

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:49:11 - - -

:58:41 THE COURT: Good afternoon.

:58:46 (Counsel respond "Good afternoon.")

:58:47 THE COURT: Please, take your seats. I apologize for the humidity. I can't do a thing about it. It's GSA. What can I say.

:58:58 Ms. Jacobs.

:59:00 MS. JACOBS: Good afternoon, Your Honor. Karen Jacobs and Ethan Townsend from Morris Nichols for the plaintiff Vanda Pharmaceuticals and Aventisub, too.

:59:10 We have here with us today from Paul Weiss Nicholas Groombridge.

:59:14 THE COURT: Welcome back, Mr. Groombridge.

:59:15 MR. GROOMBRIDGE: Thank you, Your Honor.

:59:18 MS. JACOBS: Josephine Young, Kira Davis, and Eric Stone from Paul Weiss are here at counsel table. And we have three client representatives with us today from Vanda Pharmaceuticals. We have Mihael Polymeropolous, who is the CEO, Gunther Birznieks, who is the vice president of

:59:34 1 **business development, and Vuk Koprivica, who is the**
:59:39 2 **d1irector of business development.**
:59:39 3 **(Counsel and client representatives respond**
:59:42 4 **"Good afternoon.")**
:59:42 5 **THE COURT: Good afternoon. You did well with**
:59:44 6 **those names.**
:59:45 7 **MS. JACOBS: Thank you, Your Honor.**
:59:46 8 **MR. MOORE: Good afternoon, Your Honor.**
:59:48 9 **THE COURT: Mr. Moore, how are you?**
:59:49 10 **MR. MOORE: Just fine.**
:59:50 11 **David Moore on behalf of the defendant Roxane.**
:59:52 12 **With me today from Latham & Watkins are Ken Schuler and**
:59:56 13 **Emily Melvin. Also from our client Roxane is David Don.**
:00:01 14 **THE COURT: Mr. Don, good afternoon.**
:00:05 15 **Counsel, have you talked about how you would**
:00:07 16 **like to handle this today?**
:00:09 17 **MR. GROOMBRIDGE: We have, Your Honor. We**
:00:10 18 **think, given the limited number of terms in dispute, it**
:00:13 19 **makes sense, rather than doing a ping-pong arrangement, just**
:00:16 20 **for us to go, Mr. Schuler to respond, and we may have some**
:00:20 21 **limited rebuttal.**
:00:20 22 **MR. SCHULER: I agree, Your Honor. In addition,**
:00:22 23 **I think we talked beforehand, you have allotted three hours.**
:00:26 24 **In the interests of efficiency and trying to get through**
:00:30 25 **things, we think it's no more than two hours and maybe less**

:00:33 1 **than that.**

:00:33 2 **THE COURT: I suspected as much. I may have to**

:00:36 3 **shorten a little more, because I am not going to hear**

:00:39 4 **indefiniteness arguments today.**

:00:40 5 **I may ask you a question or two regarding the**

:00:46 6 **Ellison machine motion, the 101 motion. I may rule on that**

:00:53 7 **today. Don't get nervous, plaintiff. It is something I**

:00:57 8 **want to hear, in response to my question, Mr. Schuler, I**

:01:02 9 **think it is a question for another day, quite frankly, when**

:01:09 10 **the record is fulsomely developed in a more better**

:01:14 11 **procedural posture. In a Ted Koppel kind of way, I want you**

:01:18 12 **to know what you are looking at.**

:01:20 13 **MR. SCHULER: We appreciate that, Your Honor.**

:01:22 14 **We hope to at a later day help you understand more fulsomely**

:01:26 15 **what the state of affairs is. But I think we are intending**

:01:28 16 **to do a little background for that. Perhaps that would be**

:01:32 17 **the opportune time for us.**

:01:34 18 **THE COURT: Mr. Groombridge.**

:01:35 19 **MR. GROOMBRIDGE: Your Honor, I am sure it comes**

:01:38 20 **as no surprise to the Court that we have some PowerPoint**

:01:41 21 **materials.**

:01:41 22 **THE COURT: Mr. Buckson.**

:02:36 23 **MR. GROOMBRIDGE: Your Honor, here what we had**

:02:44 24 **planned was to talk about the background of the patent and**

:02:49 25 **then to talk about the disputed terms.**

:02:51 **We suspected that the Court would probably not**
:02:54 **wants to hear about indefiniteness, so we won't cover that.**
:02:59 **Jumping right in on the patent, what the patent**
:03:02 **is about is really identification of genetic mutations or**
:03:09 **polymorphisms that are associated with the risk of something**
:03:13 **called QT prolongation when you take the drug in question,**
:03:17 **which is iloperidone, and then, flowing from that body of**
:03:23 **work, methods of treating people who have these mutations in**
:03:27 **such a way as to reduce the risk.**
:03:31 **If we go through the claim, Claim 1, exemplary,**
:03:36 **it talks about treating schizophrenia with two steps. First**
:03:43 **of all, we determine whether the patient is what's called a**
:03:46 **CYP2D6 poor metabolizer -- and Your Honor will hear a great**
:03:51 **deal of discussion about what that means, by taking -- and**
:03:54 **again, we have highlighted the terms here, for the moment I**
:03:58 **will focus on this -- taking a biological sample, and then**
:04:01 **performing or having performed a genotyping assay, in**
:04:05 **essence, DNA sequencing or something analogous, to see**
:04:08 **whether the genetic sequence says this person has the type**
:04:12 **of mutation that would make them a poor metabolizer, and**
:04:16 **then if they do have that genotype, giving them an amount in**
:04:21 **a certain range, and if they don't have that genotype,**
:04:25 **giving them a greater amount.**
:04:26 **The reason for that is that the risk of**
:04:29 **so-called QTc prolongation is lower for these people, poor**

:04:35 1 metabolizers, when you reduce the amount, as the patent
:04:38 2 explains.
:04:40 3 Sometimes we see QT prolongation, for example,
:04:44 4 in the abstract. Sometimes, for example, in the claim we
:04:47 5 see QTc prolongation. The c means corrected, and it refers
:04:51 6 to the application of certain formulae. In the context of
:04:56 7 the broader case, that may matter. I believe for today's
:05:01 8 purpose there is no difference and they are effectively
:05:01 9 synonyms.
:05:05 10 What QT prolongation is -- I apologize in
:05:08 11 advance, this is probably poorly legible -- this is the
:05:13 12 label of Fanapt. It says, "Fanapt is associated with the
:05:17 13 prolongation of the QTc interval."
:05:19 14 In other words, that prolongation is associated
:05:22 15 with the ability to cause something called torsade de
:05:26 16 pointes, a French term, arrhythmia, a potentially fatal
:05:33 17 ventricular tachycardia.
:05:34 18 So this QT prolongation is a side effect and a
:05:37 19 very potentially catastrophic side effect. Torsade de
:05:43 20 pointes, although uncommon, is terribly. It literally
:05:48 21 refers to a situation where someone may just drop dead. Of
:05:51 22 course, as you would imagine, the medical profession is very
:05:54 23 concerned to make sure they are not putting people in that
:05:56 24 situation.
:05:57 25 Thus, the backdrop to the patent was research

:06:00 1 into what is the relationship between this drug and QT
:06:07 2 prolongation.
:06:07 3 I will touch on some of what the inventors found
:06:12 4 here.
:06:12 5 I should point out, by the way, that Dr.
:06:15 6 Polymeropolous, in addition to being CEO, is one of the
:06:18 7 inventors of the patent.
:06:22 8 So the Q and the T refer to signals in the
:06:25 9 electrical activity of the heart. The Q we see here is a
:06:32 10 point in the electrical wave where the heart is full of
:06:35 11 blood. The T corresponds with the point at which the heart
:06:40 12 contracts and squeezes the blood out up through the aorta, a
:06:44 13 topic about which we heard a lot about in a prior
:06:47 14 proceeding.
:06:47 15 The prolongation here we are seeing, in the
:06:51 16 sense of the extended temporal difference here, where this
:06:55 17 is the normal QT signal and this is where it's been
:06:59 18 prolonged.
:07:01 19 In addition to torsade de pointes, there can be
:07:04 20 other negative effects from this. So it is something that
:07:07 21 physicians are quite focused on and regulatory agencies have
:07:10 22 also been quite focused on.
:07:13 23 This patent is really one of the, in our view,
:07:19 24 the first wave of patents in the personalized medicine area.
:07:25 25 In essence, as Your Honor is well aware, drugs are evaluated

:07:29 1 in terms of safety and efficacy. In any given human
:07:33 2 population, because of variations in individuals, genetic
:07:37 3 variations, some drugs, giving the same drug in the same
:07:42 4 amount to a group of people will have different
:07:44 5 consequences, different safety, difference kinetic efficacy.
:07:48 6 This patent is concerned with the safety part of that.
:07:51 7 Basically, it is saying, I am going to look at individual
:07:57 8 genetic characteristics of the patient population, and then
:07:59 9 attempt to, if you will, customize the treatment, with the
:08:05 10 goal of avoiding this harmful side effect of QT
:08:09 11 prolongation.
:08:10 12 As we get into the mechanisms that are involved
:08:12 13 here, what is going on, the reason for the way the genetic
:08:19 14 variance is causing different effects has to do with how the
:08:22 15 drugs are metabolized. Typically, when we ingest a drug,
:08:26 16 what's going on is enzymes within the body are acting on
:08:29 17 that drug and converting it into different chemicals through
:08:32 18 different metabolic pathways. Very often, indeed, in the
:08:36 19 case of the drug at issue here, iloperidone, there can be a
:08:40 20 cocktail of different metabolites. I will look at that in a
:08:44 21 minute.
:08:45 22 The metabolites may be variously therapeutic,
:08:48 23 harmful, or completely inactive. So depending on how your
:08:54 24 body or my body processes the drug, it can change the nature
:09:00 25 of that cocktail, which in turn changes the nature of the

side effect profile.

In particular, with respect to so-called psychotropic drugs, important in the metabolic mechanism, very important, is a set of enzymes that are collectively referred to as the Cytochrome P450 enzymes or frequently CYP. From here on in I will use CYP, which is an abbreviation for Cytochrome P450. We see in this pie chart this family of enzymes that are implicated in the way the body metabolizes drugs of the type to which iloperidone belongs.

The specific claims are concerned with the dark blue slice of the pie, CYP2D6. It is important, and for other aspects of the lawsuit, this may become quite important, there are a lot of other enzymes involved, including one that is mentioned in the patent, CYP3A4. But for purposes of the claim construction issues, we think it is only this one, the dark blue slice of pie, that is implicated here.

A few other terms I wanted to just touch on because they have been used by the parties in the briefing.

We are not sure -- for example, with this term, in our view, it probably doesn't really have an effect on the claim construction issues before Your Honor. But it has cropped up particularly in Roxane's briefing, and we wanted to make sure everyone is on the same page about that.

:10:43 1 I don't think there is a dispute with respect to
:10:46 2 what the meaning of what an allele is. What we see here at
:10:49 3 the top is a diagram of a piece of DNA with three mutations
:10:54 4 or polymorphisms. Each of these is known as an SNP or a
:11:01 5 "snip" or single nucleotide polymorphism. There are a
:11:04 6 variety of types of mutations we can have. I could have
:11:08 7 pieces of DNA that are missing. Pieces that are added.
:11:13 8 Pieces that are repeated twice or more times.
:11:14 9 But the most common type of mutation is this
:11:18 10 single nucleotide polymorphism, where one letter of the DNA
:11:21 11 is replaced with a different letter. Here, the one in the
:11:25 12 middle, it could be A or it could be G. That is what an
:11:30 13 SNP, or a single nucleotide polymorphism is.
:11:33 14 About 90 percent of the mutations in the human
:11:37 15 genomes are SNPs. The effect of any given one could be
:11:41 16 nothing at all, could have some kind of physiological effect
:11:44 17 that can vary under a whole lot of circumstances. We will
:11:48 18 see some of the effects as we get into what is disclosed in
:11:51 19 the patent.
:11:52 20 An allele refers to the fact that pieces of DNA
:11:57 21 can be transmitted genetically through the reproductive
:12:01 22 process as chunks, if you will. So what we see here, three
:12:07 23 alleles, the notation for designating an allele commonly
:12:11 24 uses this asterisk or star. Here we have Star 1, Star 2,
:12:15 25 and Star 3. In essence, what these are, they are

:12:18 1 **combinations of mutations. So Star 1 will have a T here, an**
:12:24 2 **A here in the middle, and a G at this end. That group will**
:12:28 3 **always travel together if you have a Star 1 allele.**
:12:31 4 **Likewise for the others. So an allele is in essence is a**
:12:35 5 **combo set of mutations.**
:12:39 6 **I also wanted to talk about genotypes and**
:12:42 7 **phenotypes, which are words that figure prominently in the**
:12:46 8 **claims and the patent. Genotypes, this is in the claims,**
:12:50 9 **not phenotype. In our view, I don't think this will be**
:12:53 10 **disputed, the terms genotype and phenotype are commonly**
:12:57 11 **used, and they are used in this patent in their ordinary art**
:13:00 12 **recognized sense. Certainly, Mr. Schuler will be able to**
:13:04 13 **confirm or dispute that.**
:13:05 14 **We think that the parties are in agreement that**
:13:08 15 **genotype and phenotype, as they are used in this patent, do**
:13:11 16 **not depart from their art recognized meaning.**
:13:14 17 **Genotype means having a particular combination**
:13:20 18 **of genetic code at a particular location. Frequently, we**
:13:24 19 **are talking about a specific gene or genetic locus. And**
:13:30 20 **whatever series of As and Gs and Cs and Ts you have in that**
:13:33 21 **region of DNA is your genotype.**
:13:37 22 **A phenotype is then the manifested consequence**
:13:40 23 **of having that genotype. It's what is the effect of that**
:13:45 24 **genotype as it is put into use by the organism, and it**
:13:51 25 **results in manifested physical characteristics.**

:13:53 1 What we see in this slide here are a number of
:13:59 2 CYP2D6 alleles, for example, Star 4 is one that we will hear
:14:06 3 about on the left-hand side, Star 10, Star 1, which, as the
:14:14 4 numbering might suggest, is the nominal or base case,
:14:16 5 sometimes referred to in this field as the biotype. Star
:14:21 6 17. Then over here, Star 2 times a factor, indicating that
:14:26 7 it's replicated, it's present in more than one copy.
:14:31 8 At the top here, we would have the genotype.
:14:38 9 With this particular mutation, referred to typically as Star
:14:42 10 4, the result of this would be a deletion that results in
:14:45 11 the enzyme not being produced. I don't know how much Your
:14:51 12 Honor would be interested in this. But as I understand the
:14:53 13 process, what that mutation means is when the protein is
:14:58 14 being assembled as a series of amino acids, following the
:15:03 15 genetic code, the mutation functions as a premature stop
:15:08 16 code. It says long before the assembly gets to the end, it
:15:12 17 stops the process and you don't get any protein in any
:15:15 18 meaningful sense.
:15:17 19 So people who have that mutation don't have
:15:20 20 CYP2D6 metabolism because they don't have the CYP2D6
:15:28 21 protein.
:15:28 22 Here you can have a different mutation that
:15:31 23 results in the formation of an unstable enzyme that gives
:15:36 24 you reduced -- you do metabolize it but you metabolize it at
:15:38 25 a lower rate. These people in the middle would be the ones

:15:41 1 **with the base case.**

:15:42 2 **It is also possible some mutations can also have**

:15:47 3 **the substrate specificity, which would mean that the change**

:15:51 4 **in the structure of the enzyme would cause it to act**

:15:53 5 **differently when it encounters the drug and it may produce,**

:15:57 6 **for example, different metabolites.**

:15:58 7 **Lastly, but by no means least, you could have**

:16:03 8 **multiple copies, in which case you produce the right enzyme**

:16:06 9 **but at higher levels, so your body processes the drug much**

:16:10 10 **faster and can produce higher levels of the metabolite in**

:16:13 11 **any given set of circumstances.**

:16:18 12 **Now, one of the other concepts I thought would**

:16:20 13 **be useful for us to talk about is the idea of what is called**

:16:24 14 **heterozygosity, not because we believe that it has a role in**

:16:30 15 **claim construction, but because it figures prominently in**

:16:33 16 **Roxane's arguments. We wanted to make sure again that**

:16:36 17 **everyone is on the same page as to at least what the basics**

:16:40 18 **are here.**

:16:41 19 **The idea of heterozygosity, the hetero, meaning,**

:16:45 20 **of course, different, is that you could have two differing**

:16:50 21 **copies of the gene. And why would you have two? Everybody**

:16:54 22 **has two copies of all of their genes. We all have, all**

:16:58 23 **human beings have 23 pairs of chromosomes. We inherit one**

:17:02 24 **of each pair from our mother and one from our father.**

:17:06 25 **In the process of reproduction of human beings**

or other organisms, what is happening is the DNA is, if you will, reshuffled. We see -- I apologize. The screen is making a poor showing of this. But if we look at the part of the slide that's labeled Mom, we see two chromosomes, one dark blue and one light blue. In the reproductive process, the first thing that happens is those get reshuffled. So you may have two blue chromosomes, but each of them is made up of some of the dark blue and some of the light blue.

The same process occurs with the father. And the offspring will receive one each of these reshuffled chromosomes. So that the DNA has now been put back together in a fashion. Because we have two chromosomes, we have two copies of each gene, and it raises the possibility that we could have different copies, if the two copies are the same, and for the vast majority of genes they will be, then we would say, well, we are homozytes for that particular gene. But if they are different, we are heterozytes for it.

What we can see here, for example, the genes that code for the proteins that are implicated in how we respond to drugs are just like all the other genes, subject to this. So we could end up, if we have a parent that has two copies of the normal gene and a parent who has one normal copy and one variant, the children could end up with either of those.

One of the questions that's raised, particularly

:18:38 1 by Roxane's arguments, is how do we characterize people who
:18:43 2 have two different copies, one normal and one, say,
:18:46 3 defective, although I don't mean any normative value,
:18:50 4 connotation in that. Roxane is saying, as I understand it,
:18:55 5 that if you are heterozytes and you have one normal copy of
:19:02 6 CYP2D6 but you also have a copy that includes one of the
:19:07 7 mutations that makes you metabolize poorly, then such a
:19:10 8 person would not be considered a, quote, poor metabolizer.
:19:14 9 And that's one of the issues before Your Honor and one that
:19:18 10 we will come to and address.
:19:21 11 I also wanted to talk about the metabolic
:19:26 12 pathways that are involved, because those in some ways are
:19:30 13 fundamental to understanding what the patent is about.
:19:34 14 We see in what at first blush is probably a very
:19:39 15 complicated slide here, certainly one, when it was shown to
:19:44 16 me, that's what I said, the various pathways that can be
:19:47 17 involved in metabolizing iloperidone.
:19:50 18 Here is iloperidone in the middle and slightly
:19:53 19 to the left. What is depicted are all of the variable or at
:19:56 20 least some of the various pathways by which the body
:19:59 21 processes iloperidone when it's introduced into the system.
:20:03 22 The patent particularly focuses on two of these. I will
:20:08 23 blow this one up.
:20:10 24 Here is the first one that is called out in the
:20:13 25 patent. The molecule iloperidone is given to the patient.

:20:17 1 **The body, through the action of the CYP2D6 enzyme, one of**
:20:22 2 **the things it will do is convert this into a metabolite**
:20:25 3 **called P94. P94 is then automatically converted into P95.**
:20:30 4 **And the patent talks about P95.**
:20:34 5 **P95 is not active therapeutically. In other**
:20:40 6 **words, the patent makes this clear, it doesn't treat the**
:20:44 7 **patient. It turns out it can't cross the blood brain**
:20:47 8 **barrier. It also is not implicated in QT prolongation,**
:20:51 9 **although it is implicated in some other side effects.**
:20:54 10 **For purposes of QT, this is simply unusual.**
:20:59 11 **The other pathway that the patent calls out is**
:21:02 12 **this one where iloperidone is converted into a metabolite**
:21:05 13 **called P88. Again, under some circumstances, I think not**
:21:09 14 **relevant for today's proceedings, it is converted back so**
:21:12 15 **there can be an equivalent reaction there. P88 is**
:21:17 16 **therapeutically active and is implicated in QT prolongation.**
:21:23 17 **Importantly, iloperidone itself is therapeutically active**
:21:26 18 **and is implicated in QT prolongation.**
:21:29 19 **There are some drugs where the drug itself is a**
:21:32 20 **prodrug, it doesn't work until the body gets to work and**
:21:36 21 **metabolizes it. Iloperidone is not in that category. It is**
:21:40 22 **already active when you take it.**
:21:41 23 **I will touch previously on some of the things**
:21:43 24 **that are in the patent.**
:21:44 25 **The inventors set out to look at the effects of**

:21:48 1 certain genetic variations in the CYP2D6 genotype and
:21:56 2 specifically how they correlated with QT prolongation. They
:22:02 3 picked two variations to look at, which are the ones, they
:22:07 4 are known as G1846A and C100T.
:22:14 5 Your Honor, what that notation signifies in the
:22:18 6 first case, Position 1846 in the gene, what would normally
:22:23 7 be a G is in fact mutated and is an A. Similarly, with
:22:30 8 C100T, C at Position 100, what would normally be a C is
:22:34 9 mutated and is a T. One of the things this patent points
:22:38 10 out here on the genotype is these notations, AA, AG and GG,
:22:43 11 what that is saying goes to the idea of heterozygosity. AA
:22:48 12 is meaning both copies have the mutation. AG is meaning one
:22:52 13 copy has it and one copy doesn't. And GG is meaning neither
:22:56 14 copy has it. The same here is true with respect to the
:23:00 15 C100T.
:23:02 16 What we are looking at here, AA is someone who
:23:05 17 is homozyte for the mutation. AG is someone who is
:23:09 18 heterozyte for the mutation. And GG is someone who doesn't
:23:12 19 have the mutation at all.
:23:14 20 What the inventors found when they did this is
:23:17 21 that at some dosage levels, the higher dosage level, they
:23:20 22 observed a correlation between the genotypes and QT
:23:26 23 prolongation which led them to do further work. What they
:23:30 24 did was to correlate the mutations with the ratio of P88 to
:23:38 25 P95, which, in other words, what they were saying is let's

:23:44 1 figure out how these genetic mutations relate to the
:23:48 2 presence of two metabolites that we know have different
:23:51 3 effects. Then after that they correlated those ratios with
:23:54 4 QT prolongation. And that work is reflected, for example,
:23:58 5 in Table 8. Here, they have got the P88 to P95 ratio. What
:24:04 6 they are telling the world here is that, when that ratio is
:24:07 7 below 2, you have a set of QT prolongations that are in what
:24:12 8 we would consider a safe or a relatively safe range. When
:24:16 9 that ratio is above 2, we have much higher QT prolongation,
:24:20 10 and that's something we certainly want to avoid.
:24:24 11 Just for completeness, there is a similar set of
:24:27 12 data where they throw iloperidone itself into the mix
:24:31 13 because it is already active and they have very comparable
:24:34 14 results. This PowerPoint is 3 instead of 2.
:24:38 15 What that led them to conclude, then, was
:24:44 16 depending on your genetic makeup, which of these mutations
:24:48 17 you have is going to impact how much of this drug you can
:24:51 18 safely take.
:24:52 19 If we get into the obviousness portions of the
:24:55 20 case, I don't doubt we will have a whole lot of discussion
:24:58 21 about whether that was or wasn't predictable. Obviously,
:25:02 22 that is not for today. That is what led to the practical
:25:04 23 application of these discoveries, was a method of treatment
:25:08 24 wherein we look at whether you have mutations and adjust the
:25:16 25 dosage or pick the dosage accordingly.

:25:19 1 **Now, unless Your Honor has questions regarding**
:25:21 2 **that, I will move into the construction of the disputed**
:25:22 3 **terms.**
:25:23 4 **THE COURT: I am ready.**
:25:25 5 **MR. GROOMBRIDGE: The first one -- there are**
:25:27 6 **really three disputes. The first one that we plan to touch**
:25:31 7 **on is "internally administering." We see the parties'**
:25:35 8 **respective constructions there. Vanda is saying we don't**
:25:39 9 **think this term needs construction in the context of this**
:25:44 10 **case, it's an ANDA case that we are not talking to a jury,**
:25:47 11 **we think this is just fine. Roxane's proposal would say it**
:25:51 12 **means physically administering.**
:25:54 13 **I would like to start off by talking about**
:25:56 14 **internally, what does the word internally bring to the party**
:26:00 15 **in this claim?**
:26:01 16 **Your Honor, as far as we can tell, there is no**
:26:03 17 **dispute over this. To our reading of the briefs, the**
:26:08 18 **parties agree that it's recognized in the medical art that**
:26:12 19 **there are various methods of administering, and that those**
:26:15 20 **can be put into a bucket that's called external and a bucket**
:26:19 21 **that's called internal. In fact, Roxane has submitted some**
:26:23 22 **extrinsic evidence on that. We don't disagree with it.**
:26:26 23 **We would say here that the purpose -- the**
:26:29 24 **classic method of external administration is topical in the**
:26:32 25 **form of an ointment, for example. Iloperidone is typically**

taken as a tablet, which would be internal, but you could be injected or otherwise.

The only significance of the word internally in this claim term is saying, we are excluding a set of techniques of administering drugs that apply to the outside of the patient's body. Nothing more than that.

Similarly, with respect to Roxane's use of the word physically, in our view, Your Honor, we can't really see any dispute here. As we would look at this, there is no way to administer a drug that is other than physical. The drug has to get into contact with the patient. I can't put the drug on a table and say, look at that. That's not administering the drug.

In our view, any form of administration is of necessity physical, and therefore this isn't bringing anything to the party. It is unnecessary.

But we don't dispute that there has to be a physical aspect. The drug has to be made, because it's internal administration, has to get into the patient.

The patent itself, when we look at it, talks about, it makes clear that no part of the invention resides in some novel form of administration. It says, I am talking about administering things in exactly the way that is known in the art and it includes, in fact incorporates by reference, a number of other patents that teach different

:28:01 1 ways of administration, different dosage forms, all of which
:28:05 2 in our view are entirely conventional. We don't think that
:28:09 3 there is any real dispute here over what the patent is
:28:16 4 telling us about administration.
:28:20 5 Where we think the dispute actually lies is in
:28:23 6 what is the meaning of the word administering. In
:28:30 7 particular, what we think the dispute is here, Your Honor,
:28:34 8 is if we actually strip away the excess from this, it comes
:28:39 9 down to a question of whether, as I think Roxane would
:28:44 10 articulate this, I think, whether a physician writing a
:28:47 11 prescription is administering or not. We don't think this
:28:54 12 is truly a claim construction issue. We think it is really
:28:57 13 a divided infringement issue following Akamai and that body
:29:02 14 of law. I certainly want to talk about that because it is
:29:05 15 one of the things that has been put before Your Honor to be
:29:08 16 decided.
:29:09 17 What we would say here, to resolve any
:29:13 18 confusion, we want to be very clear, in our view,
:29:16 19 administering means that the drug has to get into the
:29:19 20 patient.
:29:21 21 Now, if you had a situation where a physician
:29:27 22 wrote a prescription but the prescription was never filled,
:29:30 23 that would not constitute administering. But if you have a
:29:34 24 situation where I go to the doctor, my doctor gives me the
:29:39 25 prescription and says I want you to go and get this filled,

:29:41 1 take the drugs according to the instructions I am now giving
:29:44 2 you, and I do that, then that is administering, and the
:29:48 3 physician is the one who has administered the drug to me,
:29:51 4 even if he didn't tell me open your mouth; I am now going to
:29:55 5 put a pill in there. He or she, I should say.
:29:58 6 And that's the nub of this dispute.
:30:01 7 In our view, Your Honor, if we were to go
:30:05 8 through the evidence that Roxane points to here and explain
:30:08 9 why in our view it doesn't lead to the conclusion that they
:30:11 10 are advocating, where this argument seems to flow from a
:30:18 11 claim amendment that was made and then unmade during some of
:30:25 12 the prosecution that ultimately led to the issuance of the
:30:28 13 '610 patent.
:30:29 14 One of the things that happened here, I will
:30:32 15 start off, there was a rejection of a claim that had
:30:35 16 included the language administering, "administering an
:30:41 17 effective amount of an active pharmaceutical ingredient."
:30:45 18 In response to some rejections that are not germane to this,
:30:50 19 the applicant struck out that language, as we see in this
:30:55 20 slide, and instead replaced it with the language we see in
:30:59 21 Slide 35 here that talked about reducing the amount of the
:31:04 22 active pharmaceutical ingredient administered to the
:31:07 23 patient.
:31:09 24 Roxane's arguments flow from what the patent
:31:11 25 examiner then said in response to this amendment. If we

:31:15 1 look at that, what the patent examiner said was, the way you
:31:20 2 people have changed the language, I think you have actually
:31:23 3 created some ambiguity here. I think -- this is the patent
:31:29 4 examiner talking -- it is not clear whether your new
:31:32 5 language requires two doses, first at a higher level then a
:31:36 6 second one at a lower level, or whether it encompasses
:31:41 7 merely prescribing or planning to prescribe at the lower
:31:45 8 dose. Then importantly, "in view of the fact that the
:31:48 9 manipulative step of administering has been removed from the
:31:50 10 claim."
:31:52 11 We are going to have now an exchange with the
:31:55 12 examiner that refers to a claim in which the administering
:31:58 13 step had been eliminated. From that Roxane is now making a
:32:03 14 series of arguments about the ultimate claim in which the
:32:05 15 step of administering was put back in and it issued. In our
:32:09 16 view, Your Honor, that is wrong. But what we can see here
:32:13 17 is that the language that Roxane relies on is language that
:32:18 18 flowed directly from the fact that the administering step
:32:20 19 had been removed at this stage of the prosecution.
:32:23 20 Again, here is another thing that the examiner
:32:27 21 said in that same office action: Claim 1 has been amended
:32:31 22 to delete the previously recited administering step,
:32:34 23 necessitating the present rejection.
:32:37 24 And it goes on to say it's without the claim
:32:40 25 further requiring any actual administration.

:32:42 1 **In response to this, the applicant put the**
:32:47 2 **administering step back in. There was some further**
:32:50 3 **prosecution, probably not germane to this issue, then the**
:32:53 4 **claim issued.**
:32:57 5 **Roxane argues that the prosecuting attorney**
:33:01 6 **makes admissions. We disagree with that. But I think, more**
:33:06 7 **fundamentally, Your Honor, our view is that the claim**
:33:09 8 **construction can't be driven by things that the prosecuting**
:33:11 9 **attorney did or didn't say. The claim means what it meant**
:33:14 10 **the day the patent issued based on the evidence that the**
:33:19 11 **world can know about.**
:33:20 12 **Beyond that, we don't see that there is any**
:33:23 13 **inconsistency here; that it was always the intent in the**
:33:27 14 **prosecution to have a claim that does go to actual**
:33:32 15 **administration.**
:33:33 16 **The legal issue of whether the physician has to**
:33:36 17 **actually tell the patient open your mouth and I am going to**
:33:38 18 **put a pill in there or whether the physician gives a**
:33:43 19 **prescription and the patient takes it, that is still legally**
:33:48 20 **attributable to the physician, that to us is not a claim**
:33:50 21 **construction issue. That is an issue of a separate body of**
:33:53 22 **law that we will get to in the context of infringement.**
:33:56 23 **That seems to be what underlies the dispute here.**
:33:58 24 **In our view, we cited some of this in our brief,**
:34:03 25 **I don't want to dwell on the issue because I view it as**

:34:06 1 **infringement, not claim construction, but there is law on**
:34:09 2 **this. I conclude on this issue by pointing out, there is a**
:34:12 3 **case actually very recently, I guess about a week ago, from**
:34:17 4 **the District of Indiana, that goes to this exact issue,**
:34:22 5 **talking about what is the legal effect, under the Akamai**
:34:27 6 **type law, where the physician says to the patient, go fill**
:34:30 7 **this prescription and take the drug.**
:34:33 8 **In our view, Your Honor -- we will get to this**
:34:35 9 **when we come around to infringement -- but the claim**
:34:39 10 **construction, administering, we don't dispute that it means**
:34:42 11 **physically taking the drug and internally administering**
:34:51 12 **excludes external administration.**
:34:53 13 **THE COURT: I am glad to see Indiana getting**
:34:57 14 **some mention.**
:34:58 15 **MR. GROOMBRIDGE: Eli Lilly customarily files**
:35:02 16 **its cases there, despite our best efforts to tell them**
:35:05 17 **Delaware is the best place to file. I am just saying.**
:35:12 18 **I will move on to what we have characterized as**
:35:14 19 **the "having" clauses, the five of them that involve**
:35:18 20 **different verbs but the same grammatical structure. Again,**
:35:23 21 **you see here, Your Honor, on Slide 42 the parties' competing**
:35:28 22 **proposals. Again, in our view, no construction necessary.**
:35:33 23 **And you see Roxane's proposal in the right-hand column.**
:35:39 24 **I will start off with, I guess the good news is**
:35:42 25 **the parties do agree that these claim terms do not have --**

:35:45 1 an art-recognized meaning, that what we are talking about is
:35:49 2 the ordinary English language. Where we part company is
:35:56 3 what is the ordinary English language meaning of these
:35:59 4 things?
:36:00 5 Roxane's proposal in our view is, frankly, an
:36:05 6 inappropriate attempt to insert meanings that are not
:36:11 7 anywhere present and are not in any way conveyed by the
:36:14 8 ordinary language, and specifically put in this idea of
:36:18 9 personally, again, for the very clear reason of being able
:36:23 10 to argue later on that the physician didn't do it personally
:36:26 11 and therefore there is no infringement.
:36:29 12 We just don't see that as being in any way part
:36:32 13 of the ordinary meaning of this.
:36:37 14 It seems clear here that there are two relevant
:36:43 15 meanings, or two relevant connotations perhaps to this. One
:36:48 16 is temporal, that it can apply to something that happened in
:36:54 17 the past. And if we think about, for example, the situation
:36:57 18 where the genotyping was done earlier, suppose I go to the
:37:04 19 doctor and the doctor is thinking about prescribing Fanapt
:37:10 20 for me, my doctor says to me, I want you to have a
:37:14 21 genotyping test done. And I say, oh, funny you should
:37:17 22 mention that, my other doctor, my cardiologist had me do one
:37:22 23 of those. And my doctor manages to get hold of it and looks
:37:26 24 at the results and says, I see what kind of results you have
:37:29 25 here. You are a poor metabolizer. I am going to prescribe

:37:32 1 at a lower level. In our view, the claim was purposefully
:37:36 2 written to cover that.
:37:39 3 What it is driving at is the physician's
:37:41 4 decision based on your genetic status, regardless of when
:37:47 5 the finding out of the genetic status may have taken place.
:37:50 6 So there is a temporal aspect that we view as being
:37:55 7 important.
:37:57 8 There is also this causative aspect, where one
:38:00 9 of the meanings of have, it says on this slide, I must have
:38:04 10 my shoes repaired, I am going to have this delivered, I am
:38:07 11 going to have some flowers delivered to my wife, those are
:38:10 12 causative. And we think that that also is perfectly well
:38:13 13 within this meaning. There is nothing in this patent that
:38:17 14 excludes that.
:38:18 15 Given that we seem to be having a debate about
:38:24 16 whether or not commissioning somebody else to do work
:38:30 17 destroys direct infringement, then this causative meaning is
:38:33 18 something that we think may end up being important. We
:38:36 19 don't think it would be appropriate to say we are
:38:38 20 eliminating that. That is part of what is in these claims.
:38:42 21 If the doctor says, I want to have my
:38:44 22 phlebotomist take samples from you, that still is an action
:38:49 23 that is legally attributable to the doctor even though the
:38:52 24 doctor is causing somebody else to do it. In our view,
:38:56 25 there is nothing here that would in any way cut back those

two English language meanings.

Roxane points to the examiner's statement of reasons for allowance. And as I take the briefing, the argument is made that the language the examiner used in his statement of reasons for allowance in some way supports the reading in of those terms personally. In our view, Your Honor, not only is that incorrect, in fact, the examiner's language points to the exact opposite conclusion, that the language in question is articulated in the passive voice, is assayed or has been assayed. And, Your Honor, as we submit, the sole reason that the passive voice exists in the language is to have a way of articulating an idea that is agnostic as to who carried out the action.

And therefore, the fact that the examiner chose to articulate this in the passive voice points in exactly the opposite direction. It's not saying that the doctor had to do it. It's merely saying that it had to have been done.

So we would respectfully disagree with Roxane's argument.

Lastly on this point, they talk about, they point to some language, some dealings that occurred in a related application. Again, in our view, this is entirely silent on the question of who has to do this. This is temporal. In this related application, the examiner said that the determining step would encompass looking at a

:40:36 1 previously performed assay, the exact paradigm that I
:40:40 2 mentioned, we don't disagree with that. We think that is
:40:42 3 entirely true. It was deliberately written that way.
:40:46 4 That doesn't mean anything about who does it.
:40:50 5 This doesn't in some way compel the conclusion that if an
:40:53 6 individual other than the physician performs the assay, then
:40:57 7 in some way it's now the method can't be practiced.
:41:04 8 I guess I said "lastly." I do want to touch on
:41:08 9 one other thing.
:41:09 10 In the reply brief, Roxane argues that, says, in
:41:19 11 our view, under Vanda's proposal you could have a purely
:41:24 12 verbal request that can satisfy this and no physical steps
:41:27 13 are required. That's not our position. Our view here is,
:41:31 14 for example, you can't practice this claim unless a sample
:41:35 15 is actually taken and a genotyping assay is actually
:41:39 16 performed.
:41:40 17 There is this set of disputes around what I will
:41:44 18 call the divided infringement or Akamai issues, which we
:41:48 19 will have those arguments. But we are certainly not saying
:41:52 20 that merely thinking about or asking for a sample or a
:41:56 21 genotyping test somehow practices this. Thus, this argument
:41:59 22 is wholly a straw man, that in our view, Your Honor, we will
:42:06 23 get to this in the fullness of time when we talk about
:42:09 24 infringement issues. But under the very reason of the
:42:13 25 Akamai decision, it seems clear to us that where a physician

:42:18 1 embarks upon a series of steps in treating a patient that
:42:21 2 involves taking samples, getting genetic information,
:42:24 3 assessing that, and then making the prescribing decision and
:42:26 4 having the patient getting the drug and taking the drug,
:42:30 5 that constitutes infringement that is attributable legally
:42:32 6 to one actor, or the physician. Therefore, it's not a claim
:42:38 7 construction issue. It's an Akamai infringement issue.
:42:44 8 With that, unless Your Honor has questions, I
:42:46 9 would move on to the third and last dispute here.
:42:49 10 THE COURT: That's fine, Mr. Groombridge.
:42:52 11 MR. GROOMBRIDGE: This term is "CYP2D6 poor
:42:58 12 metabolizer genotype." This is the one that Roxane argues
:43:04 13 that it's indefinite, but if not indefinite then that it
:43:08 14 should be limited to one of four specific genotypes that are
:43:12 15 called out at various parts of the patent.
:43:15 16 Our focus, putting, obviously, indefiniteness
:43:20 17 not on the table today, so I will focus in terms of
:43:23 18 construction.
:43:24 19 The first thing we would say is wrong with
:43:26 20 Roxane's proposal is that it violates the presumption of
:43:31 21 claim differentiation, which of course is just a
:43:35 22 presumption, but nonetheless there are certain situations,
:43:38 23 as maligned as it may be as a presumption, there are certain
:43:40 24 situations where it applies, and in our view this is one of
:43:43 25 them. It's almost like a textbook example of it, because if

:43:47 1 we look at Claims 9 and 11, the sole difference, the sole
:43:50 2 thing that Claim 11 brings to the party is narrowing the
:43:55 3 term "CYP2D6 poor metabolizer genotype" to the four specific
:44:00 4 genotypes that Roxane would construe it as.
:44:04 5 So their construction would utterly vitiate
:44:07 6 Claim 11. It would simply have no meaning.
:44:13 7 We think, if we go back and just start with the
:44:16 8 patent, read through the patent, the answer here is pretty
:44:20 9 clear. The patent explicitly defines CYP2D6 poor
:44:27 10 metabolizers. Indeed, there is now agreement. During the
:44:29 11 meet-and-confer process the parties were able to reach
:44:33 12 consensus on this.
:44:34 13 So in our view, what we have here is a
:44:37 14 lexicographer situation, where it is undoubtedly true -- and
:44:43 15 I will show some of this in a moment -- that out in the art,
:44:47 16 before the patent, people referred to metabolizers in the
:44:52 17 number of different categories or buckets, and that
:44:56 18 sometimes they referred to them in four buckets: poor,
:44:59 19 intermediate, normal, and extensive.
:45:03 20 I think it might be the next slide, yes. The
:45:07 21 patent actually says this.
:45:09 22 I would point out, Your Honor, it is talking
:45:12 23 about phenotypes, not genotypes, which we believe is
:45:14 24 significant. But the patent says, in essence, look, the art
:45:19 25 recognizes that at a phenotypical level at least there are

:45:24 1 different types of metabolizers and there can be four
:45:26 2 categories of them.
:45:28 3 But the patent itself says, the way we are going
:45:32 4 to use the term is we are going to say people who have lower
:45:36 5 than normal CYP2D6 activity are referred to herein, in other
:45:41 6 words, in this patent, as CYP2D6 poor metabolizers. So we
:45:45 7 have defined it. However others may use this, this is how I
:45:48 8 am going to use it. In essence, Your Honor, what we see
:45:51 9 here is the patent said, we are going to divide the human
:45:54 10 population into two categories. And one of them is going to
:45:58 11 be poor metabolizers and the other is going to be not poor
:46:01 12 metabolizers. The clear delineation between the two is
:46:05 13 going to be, if you have lower than normal CYP2D6 enzymatic
:46:13 14 activity, you are a poor metabolizer. If you don't, if you
:46:15 15 have normal activity or increased activity, you are not a
:46:17 16 poor metabolizer. We simply divided the world into two
:46:20 17 groups of human beings. That, we think, is a clear and
:46:28 18 straightforward reading of what the '610 patent says.
:46:32 19 It then says, we go on, what is a CYP2D6 poor
:46:37 20 metabolizer genotype? We know what a poor metabolizer is.
:46:40 21 What is a poor metabolizer genotype? It says, it tells us
:46:45 22 it's a genotype which results in decreased activity of the
:46:48 23 CYP2D6 protein relative to wild type.
:46:54 24 Again, what it is saying if your genotype is
:46:57 25 such that in your body there is less activity of this

:47:00 1 protein compared to wild type, in other words, someone who
:47:03 2 is homozytegous for the normal mutations, with respect to
:47:09 3 G1846A has two Gs, that's our baseline, and if you have less
:47:15 4 than the activity of a person with two Gs at Position 1846,
:47:20 5 you have a genotype that makes you, with respect to that
:47:25 6 genetic locus, a poor metabolizer. It's just
:47:29 7 straightforward.
:47:30 8 The reason for that is because we are going to
:47:38 9 say that for one group, the poor metabolizer group, based on
:47:42 10 what we have learned about the correlation between how they
:47:45 11 metabolize the drug and QT prolongation, we are going to
:47:48 12 give those people a lower level of the drug.
:47:54 13 With respect to this argument that it should be
:47:57 14 construed, limited only to the four exemplary embodiments of
:48:03 15 a CYP2D6 poor metabolizer genotype, the specification
:48:06 16 expressly says, that's not what we are talking about. It
:48:11 17 says here, we have illustrated those four, but the method
:48:15 18 can be used with other genotypes that result in decreased
:48:20 19 activity.
:48:21 20 It then goes on to say, again -- we think that
:48:25 21 this could be implicated in the validity portion of the
:48:27 22 case, but it's not a question for today -- it says, the
:48:30 23 patent says, it's within the skill in the art based on the
:48:34 24 disclosure herein to identify additional CYPD26 genotypes
:48:38 25 that results in decreased enzymatic activity.

:48:44 1 **Beyond that, it then says, if you want to know**
:48:48 2 **what we are talking about, as of today, there are some 70**
:48:52 3 **variations that are known. It refers to a database of those**
:48:59 4 **variations. And the reason that the exemplary embodiments**
:49:06 5 **were picked is because they are the most common ones and**
:49:09 6 **they account for the majority of this incidence. But the**
:49:13 7 **patent is telling us, based on the information we have now**
:49:16 8 **given you, and the correlation that we have established here**
:49:20 9 **between metabolic pathways and QT prolongation, you are not**
:49:24 10 **limited just to these four genotypes. You can actually go**
:49:28 11 **and look at other genotypes and take the same teachings and**
:49:30 12 **apply them.**
:49:31 13 **Roxane is free to dispute that and to say, we**
:49:35 14 **think that that teaching is incorrect, and that there is a**
:49:39 15 **failure of disclosure, there is a written description**
:49:41 16 **problem or enablement problem. Fine. They can make that**
:49:44 17 **argument, and we will fight that when the time comes for**
:49:46 18 **fighting it. In our submission, Your Honor, what they can't**
:49:49 19 **do is say let's start off with the presumption that we,**
:49:52 20 **Roxane, are right and there is a failure of disclosure, and**
:49:55 21 **therefore the consequence is that we have to, quote, save**
:49:58 22 **the patent by construing it back to just these four**
:50:01 23 **exemplary embodiments.**
:50:02 24 **They can't engage in that kind of self-help at a**
:50:05 25 **claim construction level. That is reversing the legal**

:50:07 1 **methodology that is appropriate here. If in fact we are**
:50:09 2 **wrong and we did over-claim, there will be evidence, if they**
:50:12 3 **can prove it and prove it clearly and convincingly, they can**
:50:16 4 **win on validity.**
:50:17 5 **The right answer is the patent is perfectly**
:50:19 6 **clear about what it means when it talks about a CYP2D6**
:50:24 7 **genotype.**
:50:25 8 **With that, Your Honor, that would conclude my**
:50:27 9 **remarks, unless there are other things I could respond to.**
:50:30 10 **THE COURT: I have no questions. I will give**
:50:32 11 **you the last word, Mr. Groombridge.**
:50:34 12 **MR. GROOMBRIDGE: I appreciate it very much,**
:50:36 13 **Your Honor.**
:50:37 14 **THE COURT: Mr. Schuler.**
:50:38 15 **MR. SCHULER: Your Honor, may I approach?**
:50:45 16 **THE COURT: You may.**
:50:46 17 **MR. SCHULER: Just like Vanda, we thought it**
:50:49 18 **would be helpful. Let me see if I can work the technology.**
:51:12 19 **I rely on my children to do that in our house. I should say**
:51:17 20 **they mandate that I rely on them, because they don't want me**
:51:20 21 **to interfere with their enjoyment of certain video games.**
:51:24 22 **Your Honor, I am going to go over a little bit**
:51:27 23 **of backdrop just like Mr. Groombridge.**
:51:29 24 **THE COURT: Hopefully --**
:51:31 25 **MR. SCHULER: Not too much. Like ten slides.**

:51:33 1 **Again, we are talking about genetics. That part**
:51:37 2 **we all agree on.**
:51:39 3 **A little bit of backdrop.**
:51:41 4 **Typically, the DNA is a set of base pairs of**
:51:43 5 **these amino acids. The four that make up the DNA are**
:51:54 6 **cytosine, guanine, adenine, and thymine. Those, of course,**
:51:57 7 **then do create the DNA sections for a particular enzyme.**
:52:02 8 **When it codes or expresses the enzyme, we call that a gene**
:52:05 9 **because, obviously, there is more of the gene in there than**
:52:09 10 **that.**
:52:10 11 **I think Mr. Groombridge went over this a little**
:52:12 12 **bit. But the gene actually appears at both sides of the**
:52:15 13 **chromosomes that you inherit from the parents. That, for**
:52:22 14 **any one gene, the representation of the correspondence gene**
:52:26 15 **on each side of the chromosome is what's called the allele.**
:52:28 16 **What can happen is that -- this was exactly what Mr.**
:52:34 17 **Groombridge said -- when you have the same one on both**
:52:36 18 **sides, we are now homozygous. If they differ, if the base**
:52:41 19 **pair differs, then that would be called heterozygous.**
:52:48 20 **Here the gene that's identified is located on**
:52:52 21 **chromosome 22. It produces a particular enzyme that is**
:52:58 22 **called debrisoquine hydroxylase. And that's a pretty**
:53:03 23 **important enzyme for metabolizing a variety of drugs,**
:53:08 24 **including in the liver.**
:53:10 25 **In the backdrop of the invention, this is a**

:53:15 1 common one of the patent, we are at Slide 14, it was known
:53:19 2 before this patent that a large number of drugs are
:53:21 3 metabolized by that particular enzyme, including many common
:53:26 4 CNS drugs. One such drug that was known to be metabolized
:53:31 5 by that enzyme was, I call it "I-loperidone," maybe it is
:53:35 6 iloperidone. That is part of the backdrop of the invention.
:53:38 7 There were mutations that were known as of that
:53:43 8 same time, 2004, that would change the activity of the gene.
:53:48 9 In one of them, the Star 4, the guanine is replaced with
:53:53 10 adenine. That is also described in the '610 patent, Column
:53:57 11 5. It's talking about some prior art literature from
:54:01 12 1994-95 and 2002. But that polymorphism or some of them
:54:06 13 were associated with reduced enzymatic activity.
:54:12 14 Here we have the replacement, and the
:54:16 15 polymorphism, so to speak, of that allele. Here is another
:54:22 16 one, the Star 10 and Star 14, with cytosine being replaced
:54:25 17 with thymine.
:54:29 18 So you may see in the specification and maybe
:54:32 19 later in the case a reference to wild type, which kind of
:54:35 20 confused me when I first saw it. What it means is that you
:54:37 21 are actually completely normal. You have inherited
:54:41 22 homozygous, normally active CYP2D6, which then means you are
:54:48 23 expressing the normal amount of the enzyme and you are
:54:51 24 metabolizing what we would express as the normal rate.
:54:57 25 If it is heterozygous, then you only have one

:55:00 1 chromosome with the active gene. And you can be extensive
:55:03 2 or intermediate, because as Mr. Groombridge said, you can
:55:06 3 have multiple copies of the gene on one side or the other.
:55:09 4 So that will come up later in the case as well.
:55:13 5 Now, if you are homozygous and you don't have
:55:16 6 any active gene, you are going to be a poor metabolizer
:55:20 7 because you don't express the protein, and therefore will
:55:25 8 not metabolize the iloperidone in the manner that the wild
:55:30 9 type would.
:55:32 10 So the genotype, and that is a claim term at
:55:35 11 issue, is, it's the genetic makeup, it's the variation or
:55:41 12 the status of the genetic makeup at that particular base
:55:45 13 pair with regard to each allele.
:55:49 14 Then the phenotype is how it manifests in your
:55:52 15 body, or how it manifests.
:55:57 16 I think Mr. Groombridge put up this very excerpt
:56:01 17 late in his presentation. If you look at the '610 patent,
:56:04 18 Column 1, it says, look, there is four known phenotypes.
:56:09 19 And the phenotype is what we agreed to -- and I will come to
:56:13 20 this later -- but we agreed to that construction because
:56:15 21 that is defined in the patent. But genotype is a different
:56:19 22 concept. That is your genetic makeup.
:56:24 23 So a little bit more background.
:56:27 24 We saw a similar slide from Mr. Groombridge.
:56:30 25 The particular risk or the particular side effect that we

:56:34 1 are interested in is what we call QT prolongation. I agree,
:56:41 2 it is used as QTc or QT, but it doesn't make a difference.
:56:45 3 So the backdrop here is identify the genetic
:56:47 4 subtype, and then dose based upon the identification of the
:56:55 5 preexisting genetic subtype.
:56:57 6 So as the abstract says, we are looking for
:57:00 7 identification of genetic polymorphisms that may be
:57:03 8 associated with a risk of what's called QT prolongation. As
:57:08 9 counsel for Vanda noted, that is a potential side effect
:57:12 10 involving cardiac issues.
:57:15 11 I want to back up to Claim 14 for a second, to
:57:18 12 put it in context. We are not talking about the
:57:21 13 administration of iloperidone for what we call the typical
:57:26 14 use. That was disclosed in the prior art. As the patent
:57:29 15 acknowledges, iloperidone and its use as an antipsychotic
:57:34 16 are described in the prior art. We are talking about a
:57:36 17 subset of what we would describe as the uses of iloperidone.
:57:44 18 Now, to put it in a little more context, because
:57:47 19 these are genetic mutations, they are not -- they are
:57:51 20 somewhat rare. The available information, this is from the
:57:55 21 Fanapt label, indicates there is only a small percentage of
:57:57 22 people that have the poor metabolizer genotype, less than
:58:03 23 ten percent of the population.
:58:06 24 Mr. Groombridge put this up. I am highlighting
:58:10 25 a little different language. This is also from the

:58:12 1 **indications and usage section of the label. And what it**
:58:16 2 **says is that -- remember, we are talking about a potential**
:58:19 3 **risk of this QTc prolongation. It says, the prescriber**
:58:24 4 **should consider the finding, of course, that iloperidone has**
:58:27 5 **this potential side effect. But in many cases that would**
:58:31 6 **lead to the conclusion that you should use a different drug.**
:58:33 7 **So we go from ten percent of the population down to even**
:58:36 8 **lower because the label itself says, look, if you are in the**
:58:39 9 **zone of risk for what the claims of the patent are talking**
:58:44 10 **about, you probably should be taking a different drug.**
:58:50 11 **So unless there is any questions about the**
:58:52 12 **tutorial, I will move on to the introduction.**
:58:56 13 **I think that there are the three disputes. I**
:58:59 14 **think they are in rather stark difference on a couple of**
:59:05 15 **issues.**
:59:06 16 **I will start with the method step verb**
:59:09 17 **limitations, then I will move to internally administering,**
:59:12 18 **then lastly move to the genotype or genetic variant**
:59:17 19 **limitation.**
:59:18 20 **For the Court's convenience and maybe not**
:59:19 21 **necessarily for today, but for further consideration, this**
:59:23 22 **Slide 26 has the disputed claim limitations highlighted as**
:59:28 23 **they appear in Claim 1 of the '610 patent.**
:59:40 24 **One thing I want to get clear is I don't view**
:59:43 25 **this as an issue of infringement. I view this as how you**

:59:45 1 **construe the claim. We know that a person is practicing**
:59:48 2 **these steps. And the person performing the claim has to**
:59:51 3 **perform the various steps. That's the definition of a**
:59:53 4 **method claim.**
:59:54 5 **The question is, how do we construe what action**
:59:57 6 **is required by the person practicing the claim? And Roxane**
:00:02 7 **views this claim language as -- and takes it at face value.**
:00:07 8 **When it says that the person practicing the claim obtaining**
:00:10 9 **or having obtained a biological sample, we take that at face**
:00:14 10 **value. The physician, who is the person who is going to**
:00:16 11 **practice the method, as Mr. Groombridge said, is obtaining**
:00:20 12 **or has previously obtained a biological sample.**
:00:27 13 **Vanda, I think we heard say, they would construe**
:00:29 14 **the claim as being satisfied if the physician verbally**
:00:33 15 **requests that someone else take the biological sample. We**
:00:40 16 **would disagree with that.**
:00:41 17 **By the way, I should clarify what they said. I**
:00:44 18 **think they agree with us that it includes the physician**
:00:47 19 **doing it. They say that in addition it also includes the**
:00:51 20 **physician verbally requesting it. In the same way, for the**
:00:56 21 **performing or having performed step, we take it at face**
:01:00 22 **value that that is the person who is practicing the claim**
:01:04 23 **performs or has previously performed that.**
:01:05 24 **THE COURT: I guess face value depends upon who**
:01:08 25 **is looking at the language. You keep saying that. I, of**

course, understand your position. But I am not sure that the plaintiff would agree that that is taking it at face value.

MR. SCHULER: I understand. As I said, I wanted to clarify. I think they agree with us that it includes the physician doing this.

THE COURT: I understand that.

MR. SCHULER: They also say it encompasses something else. So I guess I would look at it as, when I am a physician and I say I want to practice this method, I would take it as, I need to perform or have previously performed a genotyping assay.

THE COURT: There is the rub, perhaps, one of them. Or have directed a genotyping assay be performed.

MR. SCHULER: I will get to that, Your Honor. I think that is not the ordinary meaning of that phraseology. I will get to the grammar that we think supports that. And I understand that at face value one might read it a different way. But we think that grammatically there is a pretty good example that they put in their brief that explains this.

Then, of course, they say there can be normal conduct.

Same thing with internally administering. We think it is a physical step. Mr. Groombridge says he

:02:21 1 agrees, it has to be physically administered. What we are
:02:24 2 saying is if you are looking at it from the perspective, I
:02:26 3 am the physician, I want to practice this claim, then I
:02:29 4 think that leads to the internally administering.
:02:31 5 By the way, if it was administering alone, there
:02:34 6 would be no dispute. I have litigated many cases where
:02:38 7 administering is the physical step. We are aware that there
:02:41 8 are plenty of cases that say administering on its own has a
:02:44 9 particular meaning. But here we have a context that's a
:02:48 10 little different. It's the addition of the internally
:02:54 11 significant rejection.
:02:54 12 They would also say that step could be satisfied
:02:57 13 by a physician verbally saying, same prescription, just take
:03:02 14 one tablet a day. The reason I say that is Fanapt, the
:03:06 15 highest dose tablet that is availability is 12 milligrams.
:03:10 16 If you are dosed at the prior art 24 milligrams a day, you
:03:13 17 are taking two of these. If you are in Claim 1 taking 12
:03:18 18 milligrams, then you would just be taking one a day. It
:03:21 19 would be the same dose and the same prescription. Just be
:03:24 20 once versus twice a day.
:03:27 21 Here we have the different physical steps. As I
:03:31 22 said, they would say, there could be three verbal steps with
:03:36 23 no direct physical action taken by the alleged direct
:03:40 24 infringer, which is the physician.
:03:43 25 The Court knows the case law. We said this just

:03:46 1 **because we are going to get to some slides. And you will**
:03:48 2 **see in the slides we tried to go through the intrinsic**
:03:50 3 **evidence and we put it in tabs, I will point that out to**
:03:53 4 **you, as to which category of intrinsic evidence we think we**
:03:57 5 **are talking about.**
:03:58 6 **So the method step limitations. I think we both**
:04:03 7 **agree that the language -- there are several of these. But**
:04:08 8 **they have a similar structure. We have the active verb or**
:04:12 9 **the past tense. So they all rise and fall together, I think**
:04:16 10 **is what we would agree with Mr. Groombridge.**
:04:20 11 **And here is the competing constructions.**
:04:28 12 **This may be where it's appropriate to discuss**
:04:30 13 **your question or questions about the 101 issue. The reason**
:04:36 14 **we bring this up is that some courts indicate they want to**
:04:40 15 **have claim construction before they look at those issues.**
:04:42 16 **THE COURT: Let me tell you what this Court has**
:04:44 17 **said on that. It's that it's not necessary to have claim**
:04:48 18 **construction before deciding the 101 issue. I recently**
:04:52 19 **decided a 101 issue, as you may know.**
:04:55 20 **MR. SCHULER: I did see that.**
:04:56 21 **THE COURT: That is not to say that will always**
:04:59 22 **be the case. I am not sure one size fits all concerning**
:05:03 23 **101. Difficult to characterize me on that.**
:05:06 24 **MR. SCHULER: It's obviously an area of the law**
:05:08 25 **that continues to evolve.**

:05:09 1 **THE COURT: It will evolve. Eventually, I**
:05:11 2 **suspect that the Fed Circuit will give us more guidance, and**
:05:15 3 **I suspect the Supreme Court will give the Fed Circuit**
:05:19 4 **further guidance on that.**
:05:20 5 **MR. SCHULER: I suspect you are right.**
:05:22 6 **The only point we were making here is that,**
:05:26 7 **there was some statement in the claim construction briefing**
:05:28 8 **by Vanda that we think kind of highlights our point, which**
:05:31 9 **is, there is no novel assay or no novel genetic test that**
:05:35 10 **they developed. It's conventional activity.**
:05:38 11 **THE COURT: I am not going to discuss that right**
:05:40 12 **now. I have a question on that subject. Let's go through**
:05:44 13 **the Markman process.**
:05:46 14 **MR. SCHULER: Fair enough, Your Honor.**
:05:48 15 **The present perfect tense is the grammatically**
:05:51 16 **correct meaning. These are the three reasons why we believe**
:05:54 17 **that Roxane's proposed construction is the appropriate one.**
:05:57 18 **The prosecution history we believe supports our proposed**
:06:00 19 **construction, and the abstraction point that I will come to.**
:06:04 20 **The present perfect tense being the plain and**
:06:07 21 **ordinary meaning, again, there is no dispute on this. It's**
:06:10 22 **helpful to discuss that with Mr. Groombridge. We both agree**
:06:14 23 **we have to look at grammar, and they do agree that the**
:06:17 24 **meaning at least encompasses the past tense or the present**
:06:20 25 **tense.**

:06:23 1 **Now, here is where I think is the clear example.**
:06:26 2 **In their briefing, they say, yes, of course, it includes**
:06:29 3 **past tense events like having graduated law school, but it**
:06:34 4 **also includes more. It includes asking someone else or**
:06:37 5 **causing.**
:06:37 6 **Let's take the claim language and put it into**
:06:42 7 **the context of, say, a job posting for a judicial intern**
:06:46 8 **position. And the language that is used in the job posting**
:06:49 9 **is, "obtaining or having obtained a law degree." Now, we**
:06:53 10 **all know what the ordinary meaning of that would be. It**
:06:55 11 **would be that you are either in law school or you have**
:06:59 12 **previously graduated from law school. It would not**
:07:00 13 **encompass asking a friend to go to law school. So when I**
:07:05 14 **say that we think that we take it at face value because it**
:07:09 15 **means two tenses, the present or past tense, first off, that**
:07:14 16 **is a pretty apt example. You don't go around saying**
:07:16 17 **obtaining or having obtained a law degree to refer to asking**
:07:20 18 **some third party to obtain a degree.**
:07:26 19 **Here is their counterexample of causation. We**
:07:29 20 **believe it doesn't actually correspond to the claim**
:07:33 21 **language. I will explain why in the next slide.**
:07:35 22 **The causative use of have occurs when you have**
:07:39 23 **"have" plus the object. Here you can see at the top the**
:07:44 24 **three -- let me see if I can do the pointer -- the three**
:07:47 25 **verbs at the top are laughing, prepared, and stolen. Those**

:07:52 1 come after the object. Here, you have two verbs, performing
:07:56 2 or having performed, present tense, past tense, and then the
:08:01 3 object.
:08:02 4 So this isn't phrased in the causative, and
:08:05 5 that's why the law school, obtaining or having obtained a
:08:08 6 law degree, is understood by those in English as meaning you
:08:14 7 personally have done so.
:08:16 8 Now, the other point we make, Slide 46, is that
:08:22 9 effectively they are rewriting the claim language. They are
:08:25 10 asking the Court to construe the language as meaning
:08:28 11 obtaining or requesting a biological example. I emphasize
:08:30 12 that because they could have claimed that. That could have
:08:35 13 been the language they included. We are going to see that
:08:37 14 they had to put different language in in order to overcome a
:08:40 15 rejection. And had they done so, we would say they can't
:08:43 16 rewrite the claims under the guise of claim construction.
:08:46 17 But they easily could have clarified that they
:08:49 18 meant obtaining or requesting a biological sample, and that
:08:53 19 would have made entire sense. But they did not. So the
:08:56 20 words they did choose should be given their grammatical
:09:00 21 ordinary meaning.
:09:04 22 Here is the tabs, by the way, Your Honor, to
:09:06 23 clarify. You see at the top, we have got the claim
:09:08 24 language, then we have a tab for the specification, then one
:09:13 25 for the prosecution history.

:09:14 1 **We said this in our briefing and I will say it**
:09:16 2 **again today. Except for the final limitation of the**
:09:19 3 **genotype, there is really not much the specification says**
:09:22 4 **that's pertinent to either of the other two disputes. It's**
:09:25 5 **really the prosecution history and claim language itself.**
:09:30 6 **So we have their point that it is not limited to**
:09:34 7 **that and that it could be requesting.**
:09:37 8 **But I guess the point we are making here is,**
:09:40 9 **they do make a plea for ordinary meaning and that it need**
:09:44 10 **not be construed. I think, in light of 02 Micro, that can't**
:09:47 11 **really hurt. Even if the Court agrees that both sides have**
:09:51 12 **some support in English grammar, in other words, that there**
:09:55 13 **could be two ordinary meanings here, then 02 Micro suggests**
:09:59 14 **you have to then choose one because you have to get further**
:10:05 15 **guidance to resolve the dispute. Vanda's request is simply**
:10:08 16 **we invoke the ostensible ordinary meaning. That may not be**
:10:13 17 **sufficient.**
:10:14 18 **THE COURT: Doesn't the 02 Micro decision leave**
:10:20 19 **the judges with the discretion that there really is not a**
:10:24 20 **dispute?**
:10:24 21 **MR. SCHULER: Correct. I read the case as**
:10:27 22 **saying if there is a legitimate dispute, which I think there**
:10:29 23 **is here, I think we are saying here is the ordinary meaning,**
:10:31 24 **and they are saying that is the ordinary meaning plus.**
:10:34 25 **THE COURT: I can still say, no, I don't really**

:10:37 1 **buy that there is a dispute.**

:10:39 2 **MR. SCHULER: Correct. If there is a legitimate**

:10:40 3 **dispute, I think --**

:10:42 4 **THE COURT: And have done my job of claim**

:10:45 5 **construction.**

:10:46 6 **MR. SCHULER: Yes.**

:10:50 7 **Now, the prosecution history, which we do**

:10:53 8 **believe is, beyond the grammar, the other salient evidence**

:10:56 9 **here.**

:10:56 10 **I am going to go through this in a few steps. I**

:11:00 11 **think Mr. Groombridge did it in a couple of slides. But I**

:11:03 12 **think it is important to have the context.**

:11:05 13 **They added these two limitations during the**

:11:10 14 **course of prosecution. And the examiner then said that it**

:11:18 15 **requires steps in which the genotype has been assayed -- is**

:11:23 16 **assayed or has been assayed. We think there is two salient**

:11:28 17 **points that come out of that. The first is the examiner is**

:11:32 18 **a person of ordinary skill in the art. He understands that**

:11:35 19 **the claim language is consistent with what we say is the**

:11:38 20 **ordinary meaning in the present perfect tense, where there**

:11:41 21 **is two tenses, the present, and the past, that is exactly**

:11:45 22 **what he said, "is assayed" in the present tense or "has been**

:11:48 23 **assayed" in the past tense. And that is a step that is**

:11:51 24 **occurring or occurred in the past.**

:11:53 25 **Second, the examiner does not say that the steps**

:11:57 1 **can include the future, a request that a third party do so**
:12:01 2 **in the future. But that is what Vanda proposes the ordinary**
:12:04 3 **meaning is. And, to be honest, Your Honor, I am not sure of**
:12:09 4 **an English phrase that I am aware of that would convey all**
:12:12 5 **three tenses. That's what they are saying. They are**
:12:15 6 **saying, we agree it's the present tense, we agree it's the**
:12:18 7 **past tense, we want you to imply that it's also the future**
:12:22 8 **tense.**
:12:23 9 **I am not aware of this language having that**
:12:25 10 **meaning, and I am not sure I am aware of any English**
:12:28 11 **language phrase that has those to three meanings. But the**
:12:32 12 **examiner, who is a person of ordinary skill in the art,**
:12:35 13 **appears to agree with us that it is two tenses, the present**
:12:38 14 **or the past.**
:12:39 15 **Now, the abstraction point -- the reason we say**
:12:46 16 **this is not just because we think it's abstract but we think**
:12:49 17 **it dovetails with the prosecution history. Again, their**
:12:53 18 **proposal is that it could include verbal steps, the**
:12:55 19 **physician directly asking someone to obtain a biological**
:12:59 20 **sample and assay that for the genetic subtype.**
:13:03 21 **Now, during prosecution they got a rejection and**
:13:06 22 **they got a rejection under 101 not because of the law of**
:13:13 23 **nature issue but because of the abstractness. Their**
:13:17 24 **response was to say, look, we require now a biological**
:13:20 25 **sample in performing a manipulative step, and also a**

:13:25 transformative method of performing the assay on that
:13:27 biological sample and establishing both the genetic subtype
:13:32 and the phenotype.
:13:37 That is what we believe, that these are physical
:13:39 steps and they are not verbal steps.
:13:48 I want to step back a second, Your Honor.
:13:51 This occurred to me as I was preparing. They
:13:55 are effectively saying, yes, we agree that if a physician
:13:57 personally did these things, that would be practicing the
:13:59 method. But they are also saying that if a physician
:14:03 verbalizes certain statements, that they would be liable as
:14:06 a direct infringer. And that would seem to us to implicate
:14:10 the potential for interference with the First Amendment.
:14:14 The First Amendment, under the First Amendment
:14:16 there would be tort-like liability for patent infringement
:14:19 if a physician uttered a certain sequence of words under
:14:22 their proposed construction.
:14:26 I guess between two competing constructions, one
:14:28 that says we request that it be construed to be physical
:14:32 acts, which is Roxane's, versus one that says physical acts
:14:36 plus a certain sequence of words, we think the better
:14:39 construction would be the one that would not implicate the
:14:42 First Amendment, because this is speech. This is not
:14:46 hateful, it's not false, it's not defamatory.
:14:50 They would say if a physician says a certain

:14:53 1 **sequence of words, that they could potentially be a direct**
:14:56 2 **infringer. We think, between the two constructions, that's**
:14:59 3 **an additional reason that it would be better to construe**
:15:02 4 **them the way that Roxane suggests.**
:15:06 5 **The other point of the prosecution history.**
:15:07 6 **They had an interview. They had an existing claim that had**
:15:12 7 **been rejected. This is at the top. You can see the**
:15:15 8 **interview summary.**
:15:16 9 **The examiner says, look, right now they only**
:15:18 10 **require a single active step of internally administering**
:15:22 11 **iloperidone. But outside of dosage, it is already talked**
:15:26 12 **about in the prior art. In order to get over my rejection,**
:15:28 13 **you are going to have to add further active step or steps,**
:15:32 14 **and even suggest which ones, he says there in Claim 63.**
:15:36 15 **The result was, Vanda agreed. To get over the**
:15:39 16 **rejection they added two more active steps of the claim**
:15:44 17 **language in issue.**
:15:47 18 **In the end, we know that the construction that**
:15:51 19 **stays true to the claim language and aligns best with the**
:15:54 20 **intrinsic evidence is the one that is probably the best.**
:15:56 21 **While we acknowledge that Vanda criticizes our construction**
:15:59 22 **and critiques our evidence, we do at least have various**
:16:04 23 **intrinsic evidence supporting our construction -- the claim**
:16:07 24 **language, the plain usage of grammar, and the prosecution**
:16:12 25 **history.**

:16:13 1 **Vanda, you know, for its part, does criticize**
:16:17 2 **our construction, but I am not sure what affirmative**
:16:20 3 **intrinsic evidence they would point to as supporting their**
:16:24 4 **proposed construction.**
:16:25 5 **So that's why we think, for those reasons,**
:16:29 6 **Roxane's proposed production should be adopted.**
:16:32 7 **Unless the Court has any questions on that, I am**
:16:34 8 **going to move to the internally administering.**
:16:36 9 **THE COURT: You can move on.**
:16:40 10 **MR. SCHULER: As I said before, if this was**
:16:41 11 **administering, there would be no dispute. We have a dispute**
:16:46 12 **because they suggest that again no construction is**
:16:50 13 **necessary, but they say, i.e., not externally, whereas we**
:16:53 14 **say physically administering iloperidone to a patient.**
:16:59 15 **The reasons that we say that are really twofold.**
:17:02 16 **Our construction we believe is supported by the intrinsic**
:17:04 17 **evidence. The amendment that led to this term being**
:17:07 18 **included has to be given meaning. And I don't think their**
:17:11 19 **attempt at harmonization really does harmonize the claim in**
:17:15 20 **the way that they would like.**
:17:17 21 **Then lastly, we think their construction is a**
:17:20 22 **bit circular.**
:17:22 23 **The amendment then must be given meaning. We**
:17:25 24 **saw a little bit of this previously from Mr. Groombridge.**
:17:28 25 **Here is what happened. They did, they deleted**

:17:31 1 **administering, and replaced it with reducing. So the active**
:17:35 2 **step was reducing, except the examiner said, I am not sure**
:17:39 3 **that is an active step and so I am going to issue a 112**
:17:44 4 **rejection because I am not sure whether the claim in fact**
:17:46 5 **encompasses merely prescribing because you eliminated the**
:17:49 6 **manipulative step of administering. This is why I say, Your**
:17:52 7 **Honor, if administering were the only word, I wouldn't**
:17:54 8 **disagree with them, because the examiner understood**
:17:58 9 **administering on its own would be prescribing. But he said**
:18:01 10 **I don't know if that's enough. I don't know if that's**
:18:03 11 **enough -- I don't know what it means. I don't know what the**
:18:05 12 **claim means now.**
:18:06 13 **The response was not to -- we heard Mr.**
:18:09 14 **Groombridge say, it was a statement or a word that was made**
:18:11 15 **and unmade. But I am not sure I quite agree with that,**
:18:15 16 **because they didn't just put administering back in the**
:18:17 17 **claim. They could have. And they could have, in fact,**
:18:20 18 **said, yes, we do clarify, we do mean to include prescribing.**
:18:24 19 **But they did something different and they did something, we**
:18:26 20 **think, different for a reason.**
:18:28 21 **They said, if the patient's a poor metabolizer**
:18:32 22 **genetic subtype, then internally administering the**
:18:36 23 **iloperidone. They did more than that, though. They told**
:18:39 24 **the examiner, now that we have included internally**
:18:43 25 **administering, these claims which recite, quote, "internally**

:18:48 1 **administering," end quote, stop, thus tying the method to**
:18:52 2 **the particular drug and dosage to be administered and thus**
:18:56 3 **eliminating the basis for this rejection.**
:18:57 4 **We know that this claim limitation that was**
:19:00 5 **added has to have some substantive meaning because it's what**
:19:03 6 **they used to get around the rejection.**
:19:10 7 **Following that course of conduct, what do we**
:19:12 8 **have?**
:19:13 9 **Vanda says, and we don't disagree, administering**
:19:16 10 **describes the typical activities of doctors in prescribing**
:19:21 11 **drugs. That is the well-known, ordinary meaning of the word**
:19:24 12 **administering in isolation. But they say even after the**
:19:26 13 **amendment to the internally administering, it still includes**
:19:29 14 **writing a prescription. So it's not clear to us how it was**
:19:34 15 **narrowed, if you adopted their construction.**
:19:36 16 **But again, they did delete administering, and**
:19:45 17 **instead added internally administering.**
:19:48 18 **Now, under Festo, which we are all well aware**
:19:50 19 **of, there is a presumption now that because there was a**
:19:54 20 **rejection, a claim amendment, the presumption is that the**
:19:57 21 **claim is not as broad as it was before. And the other**
:20:02 22 **presumption, of course, the Court is well aware of is we are**
:20:05 23 **supposed to give, the parties are supposed to give meaning**
:20:08 24 **to every term in a claim.**
:20:10 25 **But again, if it is merely prescribing, we are**

:20:13 1 **not sure that that is true.**

:20:16 2 **Now, Vanda then attempts to say we can harmonize**

:20:19 3 **this. The harmonization is that we only meant to take out**

:20:25 4 **topical or external routes of administration.**

:20:29 5 **But there is a couple of issues with that. The**

:20:33 6 **first is -- look at some of the admitted, and some of this**

:20:37 7 **is intrinsic, I think -- admitted routes of internal**

:20:40 8 **administration. Intravenous, and perhaps most interestingly**

:20:43 9 **we have highlighted here intraspinal. You do not get**

:20:47 10 **prescriptions at CVS to go give yourself a spinal injection.**

:20:51 11 **Those are physical acts by doctors. Those are methods that**

:20:55 12 **are only done typically at a hospital by a physician.**

:20:58 13 **So that evidence supports our point that when**

:21:03 14 **you are talking about internal administration, you are not**

:21:05 15 **talking about merely prescribing. You are talking about a**

:21:07 16 **physical act by a physician to make sure that the drug gets**

:21:11 17 **into the body.**

:21:13 18 **The second point is, there harmonization might**

:21:18 19 **make some sense if the examiner was saying I don't quite**

:21:21 20 **understand, does administering mean topical or does it mean**

:21:23 21 **oral? That wasn't his confusion.**

:21:26 22 **He didn't say I am rejecting this because I**

:21:30 23 **don't know how many routes of administration you are**

:21:31 24 **covering. He rejected it because he wasn't sure that**

:21:34 25 **prescribing was included or not or whether that was enough**

of a manipulative step.

And the response -- therefore, just saying that the amendment simply eliminated topical administration doesn't really dovetail with the manner in which the claim amendment occurred.

The other reason why we think the prosecution history supports us is to go back to that interview summary, Your Honor. Let's look at how the examiner characterized the step. Even though he said it wasn't enough to get a patent, he said it was obvious. He still characterized it as an active step of internally administering iloperidone. Again, we are talking about who is undertaking that active step. We are talking about the person practicing the method. The person practicing the method has to take an active step of internally administering iloperidone.

That is not prescribing. Prescribing is passive. Active means the actor who is performing the method takes an active step.

So the person of ordinary skill in the art, again, this is corroborative evidence, that a person of ordinary skill in the art, the examiner, is viewing the claim the way Roxane does, that he thinks performing the method requires the active step of actually internally administering.

Then lastly, Your Honor, we think their proposed

:23:00 1 **construction is a bit circular. I know they are saying it's**
:23:02 2 **plain meaning and doesn't need a construction. But they do**
:23:08 3 **say, in plain and ordinary meaning, i.e., not externally.**
:23:10 4 **But if you look at it from the perspective of**
:23:13 5 **the person that they are saying is the direct infringer, the**
:23:16 6 **physician, writing a prescription is an entirely external**
:23:19 7 **act with regard to the patient. There is nothing internal**
:23:21 8 **about it.**
:23:24 9 **Even under their construction, we are not sure**
:23:27 10 **how it encompasses what they say.**
:23:31 11 **So again, we kind of come back to the first**
:23:34 12 **principles, we are supposed to look at the intrinsic**
:23:37 13 **evidence and see which construction best aligns with that**
:23:39 14 **intrinsic evidence. And here, we have on Roxane's part, we**
:23:44 15 **believe the claim language has that ordinary meaning, and**
:23:48 16 **the prosecution history, we think, emphasizes that ordinary**
:23:52 17 **meaning, particularly in light of the amendment and the**
:23:57 18 **corresponding statement by the examiner.**
:23:59 19 **For their part, again, Vanda criticizes our**
:24:04 20 **construction and critiques our evidence. But I am not sure**
:24:07 21 **what affirmative evidence they have, and we don't think**
:24:09 22 **whatever affirmative intrinsic evidence they have is**
:24:12 23 **compelling.**
:24:17 24 **Now, with that, I can move to the last one. But**
:24:19 25 **effectively, Your Honor, we only have one slide on this in**

:24:23 1 terms of just preserving our indefiniteness. We understand
:24:26 2 the Court will take that up at trial.
:24:28 3 With regard to our backstop position,
:24:31 4 alternative construction, we have briefed that. I am happy
:24:36 5 to answer any questions the Court has. Really, since it's
:24:38 6 our backup position --
:24:40 7 THE COURT: I have read the briefs. I am fine.
:24:43 8 MR. SCHULER: If the Court has a question about
:24:45 9 the 101, I am happy to answer that now. Otherwise, I will
:24:48 10 sit down.
:24:49 11 THE COURT: Let's take a quick too-much-coffee
:24:51 12 break and we will come back and talk a little bit about 101.
:24:55 13 (Recess taken.)
:31:02 14 THE COURT: Thank you. Please, take your seats.
:31:05 15 I am not going to detain you long.
:31:08 16 To be fair, you came here today for Markman, not
:31:11 17 to argue 101. But I guess, Mr. Schuler, to be fair, you are
:31:18 18 swimming upstream on this issue with me. I feel it
:31:24 19 appropriate -- and it's your motion -- to ask simply one
:31:30 20 question. It comes from the assertions by Vanda at Page 12
:31:38 21 of their opposition.
:31:44 22 Mr. Groombridge, do you have that with you?
:31:47 23 MR. GROOMBRIDGE: I have to confess, Your Honor,
:31:48 24 I don't have it with me.
:31:48 25 THE COURT: Mr. Schuler, do you have it?

:31:51 **MR. SCHULER: I didn't bring it with me.**

:31:52 **THE COURT: That is why I said, to be fair to both sides. But to be unfair, I am going to rule, so you will understand.**

:32:02 **Here is what is written at Page 12 under II. It's, "Roxane's motion should be denied because Roxane has failed to submit any evidence at all to satisfy its burden."**

:32:16 **Then counsel also goes on to write, "Roxane's motion should be denied because Roxane has not even tried to meet the burden it has placed on itself to secure dismissal. Roxane must show that the claims of the '610 patent do nothing more than embody a law of nature and add routine and conventional and technical steps and must make a showing so powerful and indisputable that no reasonable trier of fact could conclude otherwise."**

:32:41 **And they cite the Unicon case, quoting from Ultra Mesh. In the next paragraph they write:**

:32:47 **"In the face of this tall burden, Roxane has submitted...nothing, not a document, not a declaration, nor a scrap of evidence of any kind. Its lawyers have simply declared," this is where the rubber sort of meets the road for me, "Its lawyers have simply declared what they wrongly believe to be a law of nature and have declared," and I love it when you guys do it, "ipsi dixit, the steps of the '610 patent claims are routine and conventional.**

:33:20 1 **"That lawyer argument cannot substitute for**
:33:22 2 **evidence. Roxane assumed the burden when they filed this**
:33:25 3 **motion but has not even tried to meet it. Its motion should**
:33:29 4 **be denied."**
:33:30 5 **That for me is the essence. They could have**
:33:33 6 **written one page for CLS purposes and satisfied my concerns,**
:33:42 7 **at this stage of these proceedings, were I to dismiss the**
:33:48 8 **plaintiffs' complaint, that I would be committing reversible**
:33:52 9 **error. Not that I am afraid of committing reversible error.**
:33:57 10 **Any District Judge that is shouldn't be a District Judge.**
:34:00 11 **What is your reaction?**
:34:02 12 **MR. SCHULER: My reaction is we actually**
:34:03 13 **anticipated that the Court might want additional proof and**
:34:06 14 **we are in the process of gathering it not only through fact**
:34:09 15 **discovery but through experts. I certainly understand the**
:34:12 16 **Court does not want to place itself unduly in the position**
:34:15 17 **of a physician as to what is conventional or unconventional.**
:34:18 18 **The reason that we filed it was simply that**
:34:20 19 **there was such powerful language from Mayo, from the Supreme**
:34:23 20 **Court, that was very close in terms of what they**
:34:26 21 **characterize as conventional activity. However, I**
:34:29 22 **acknowledge, they had a record before them, and I know this**
:34:32 23 **Court will probably want to have a record before it.**
:34:34 24 **THE COURT: I was going to point that out. Go**
:34:36 25 **ahead.**

:34:37 1 **MR. SCHULER: We intend to absolutely provide**
:34:40 2 **evidence. What would help us is to understand what type of**
:34:44 3 **evidence beyond simply maybe a physician explaining what**
:34:48 4 **they believe to be routine that the Court might look to one**
:34:51 5 **way or the other.**
:34:52 6 **THE COURT: It may come to pass -- have we set**
:34:56 7 **up in this case a summary judgment schedule for requesting**
:35:00 8 **permission?**
:35:01 9 **MR. GROOMBRIDGE: We have not, Your Honor, to my**
:35:01 10 **knowledge.**
:35:04 11 **MS. JACOBS: We have not, Your Honor, because**
:35:06 12 **it's a Bench trial.**
:35:07 13 **THE COURT: It may come to pass -- I will think**
:35:11 14 **about this, because I am going to deny your motion today. I**
:35:17 15 **don't think that you have met the burden of proof by clear**
:35:21 16 **and convincing evidence on its face.**
:35:29 17 **Give me an opportunity to think some more about**
:35:31 18 **it. I may issue an order at some stage along the discovery**
:35:36 19 **road prior to, sufficiently in advance of your preparing**
:35:43 20 **your final pretrial order and getting ready for trial that**
:35:48 21 **you would still -- we would all realize some economies of**
:35:53 22 **scale, you, most especially, your clients, in having me**
:35:56 23 **revisit the issue on a more fulsome record.**
:36:03 24 **I will even add this: that if you care to have**
:36:09 25 **a meet-and-confer, I would actually not if you care to, I am**

:36:14 1 going to direct that you have a meet-and-confer at some
:36:17 2 point along the line to see if you can't agree on if this
:36:22 3 matter should be teed up again and if so just how. Probably
:36:27 4 in the form of summary judgment, I would imagine.
:36:31 5 I am going to invite you to the case management
:36:34 6 process a little bit in this way. It's not an insignificant
:36:38 7 issue. But again, to repeat myself, it's not one that I am
:36:42 8 prepared to decide at the pleading stage in your favor.
:36:47 9 MR. SCHULER: Understood, Your Honor.
:36:48 10 THE COURT: Counsel, is there anything else
:36:51 11 today while you are here we need to talk about?
:36:54 12 MR. GROOMBRIDGE: Your Honor, I don't believe
:36:55 13 there is anything else from us.
:36:58 14 I was going to simply ask --
:37:00 15 THE COURT: I am sorry. You hadn't had a chance
:37:04 16 to respond to the Markman arguments.
:37:07 17 MR. GROOMBRIDGE: I am going to ask Your Honor
:37:09 18 whether there was anything on which further response would
:37:11 19 be helpful.
:37:11 20 THE COURT: I saw you taking notes. If there is
:37:14 21 something that you would like to react to, I am sorry,
:37:17 22 please do.
:37:18 23 MR. GROOMBRIDGE: Running very briefly through
:37:19 24 my notes, on 02, our issue is that it's -- the Court, our
:37:25 25 belief is that the Court is entirely within its rights to

:37:28 1 **say I don't think there is an issue that requires**
:37:30 2 **resolution. This is certainly not -- 02 is a jury context.**
:37:34 3 **This is absolutely not that.**
:37:37 4 **There is a sort of common thread that runs**
:37:39 5 **through the arguments, saying you are trying to impose**
:37:44 6 **patent infringement liability on purely verbal activity and**
:37:48 7 **so on. I reiterate, that is not our position.**
:37:51 8 **Our position is that the genotyping, the samples**
:37:54 9 **have to be taken, the genotyping has to be done, the patient**
:37:57 10 **has to actually receive the drug.**
:38:00 11 **The legal question as to whether those can be**
:38:03 12 **legally attributed to the physician that set the process in**
:38:06 13 **motion is to us an infringement issue and not a claim**
:38:10 14 **construction issue.**
:38:12 15 **I was intrigued to hear Mr. Schuler say that if**
:38:16 16 **the only claim term were administering he would agree with**
:38:19 17 **us. It seemed to us the right way to analyze this is to**
:38:25 18 **start with administering and then say, does the addition of**
:38:28 19 **the limitation internally change anything there? And in our**
:38:33 20 **view, the extrinsic evidence, Your Honor, that Roxane itself**
:38:38 21 **submitted makes it perfectly clear that it doesn't change**
:38:42 22 **anything with respect to, for example -- I was quite taken**
:38:46 23 **with Mr. Schuler's Slide 72, which talks about all the**
:38:51 24 **things that are known as internal administration, the first**
:38:56 25 **of which is oral.**

:38:59 1 **So it may be that there is some like intraspinal**
:39:02 2 **done differently, although frankly, in our view, usually,**
:39:06 3 **when, for example, an epidural is given in connection with**
:39:10 4 **delivering a baby it is typically not done by a physician.**
:39:13 5 **THE COURT: I was going to make that**
:39:16 6 **observation.**
:39:17 7 **MR. GROOMBRIDGE: In our view, prescribing most**
:39:23 8 **certainly is an active act. And we would think that doctors**
:39:28 9 **would be probably strongly in disagreement if someone were**
:39:33 10 **to say that deciding on treatment regimen for your patient**
:39:35 11 **is not the active practice of medicine.**
:39:39 12 **So those were the main points.**
:39:42 13 **Your Honor, I don't think that there is really**
:39:44 14 **anything that we didn't cover up front. Unless the Court**
:39:48 15 **has questions...**
:39:51 16 **THE COURT: Discovery is moving along well?**
:39:54 17 **MR. SCHULER: Yes, Your Honor. I think**
:39:57 18 **technically it concluded. But we had asked you for an**
:40:00 19 **extension and we got it. There was just one or two**
:40:02 20 **depositions that for scheduling reasons, these are busy**
:40:05 21 **executives that we are finishing. It is very cooperative.**
:40:08 22 **We are getting everything done. Appreciate the Court's**
:40:10 23 **opportunity to let us think about addressing the 101 issue**
:40:15 24 **in the future.**
:40:16 25 **MR. GROOMBRIDGE: I would certainly not**

:40:18 **characterize this as a contentious case in terms of the**
:40:21 **relationship between the lawyers.**
:40:22 **THE COURT: And, Mr. Schuler, I am not going to**
:40:24 **promise you that I am going to reconsider, even once you**
:40:28 **present a more fulsome record, as I have described it, the**
:40:33 **101 issue. But there is a possibility.**
:40:35 **MR. SCHULER: Appreciate it, Your Honor.**
:40:36 **THE COURT: Counsel, safe travels.**
:40:39 **(Counsel respond "Thank you.")**
:40:39 **(Court recessed at 3:40 p.m.)**
:40:41
:40:41 **- - -**
:40:41 **Reporter: Kevin Maurer**

EXHIBIT B

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

INO THERAPEUTICS LLC and IKARIA, INC., Plaintiffs, v. PRAXAIR DISTRIBUTION, INC. and PRAXAIR, INC., Defendants.	)	Civ. No. 2015-cv-00170 (GMS)

DECLARATION OF GEOFFREY L. ROSENTHAL, M.D. PH.D.
IN SUPPORT OF PLAINTIFFS' OPPOSITION TO DEFENDANTS'
MOTION FOR JUDGMENT ON THE PLEADINGS

1. I am a Professor of Pediatrics and Epidemiology at the University of Maryland School of Medicine in Baltimore, Maryland. I have been at the University of Maryland since July 2009. I have had both academic and hospital-based roles at the University of Maryland School of Medicine and the University of Maryland Children's Hospital. The academic roles include Chair of the Division of Pediatric Cardiology (2009-present) and Chair of Pediatric Critical Care Medicine (2009-2014). In these roles I have had responsibility for faculty development, research, and training in several content areas, including training pediatric cardiologists and pediatric critical care physicians and nurses in the management of pulmonary hypertension in neonates, infants, older children, and certain categories of adults (specifically, adults with congenital heart disease).

2. I have been a practicing pediatric cardiologist since 1998. Since 1998, I have cared for over 7,000 children. My clinical area of expertise is Pediatric Cardiac Intensive Care, so my experience has been enriched over the arc of my career with neonates and children who are critically ill due to conditions related to their hearts and blood vessels. Neonates and children with critical illness due to the heart and blood vessels often have elevated resistance in the blood vessels which carry blood to the lungs, and they often have pulmonary hypertension. I am very familiar with the use of inhaled Nitric Oxide ("iNO") and other vasodilators in the neonatal and pediatric population.

3. Prior to joining the University of Maryland School of Medicine, I served as the Director of Inpatient Medicine for Pediatric Cardiovascular Services and Director of Pediatric Cardiovascular Research at the Cleveland Clinic. While at the Cleveland Clinic, I developed inpatient services for the Pediatric and Congenital Heart Center and started the Pediatric Cardiology Fellow's Clinic. In these roles I both recommended use of iNO and other

vasodilators for neonates, infants, and children in need of these therapies, and I taught both Pediatric Cardiology and Pediatric Critical Care physicians to use these agents properly. Before joining the Cleveland Clinic, I served at Seattle Children's Hospital where I started the Pediatric Cardiac Intensive Care Program. In this role I prescribed iNO and other vasodilators for neonates, infants, and children in need of these therapies, and I taught Pediatric Critical Care physicians to use these agents properly.

4. I received my undergraduate degree in psychology from Boston University, a master's degree in biostatistics and epidemiology from Georgetown University, a medical degree from the University of Maryland School of Medicine and a doctor of philosophy degree in epidemiology from the University of Maryland Graduate School. I completed my pediatric residency, neonatology chief residency, pediatric cardiology fellowship, and perioperative fellowship in pediatric cardiology at Baylor College of Medicine/Texas Children's Hospital. I am licensed to practice medicine in Maryland, and am certified by the American Board of Pediatrics in General Pediatrics and Pediatric Cardiology. I am certified by the American Board of Internal Medicine in Adult Congenital Heart Disease.

5. I have been asked to provide this declaration in support of Plaintiffs' Opposition to the Defendants' Motion for Judgment on the Pleadings.

6. Plaintiffs' INOmax® product is approved for the administration of inhaled nitric oxide to neonates suffering from hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension. Hypoxic respiratory failure is associated with abnormally low levels of oxygen in the bloodstream. Pulmonary hypertension refers to high blood pressure in the vessels going to the lungs. Persistent pulmonary hypertension in neonates (PPHN) results when the pulmonary vessels fail to adequately relax and

there is insufficient gas exchange. In these patients, iNO relaxes the small vessels that are in close proximity to the aerated parts of the lungs and allows for increased effective blood flow to the lungs. The increased blood flow following iNO administration improves oxygenation and reduces the need for other therapies known to be associated with very high risk of complications and morbidity, such as aggressive ventilation strategies, administration of oxygen concentrations associated with ocular toxicity, and use of extracorporeal membrane oxygenation.

7. Administering iNO to certain neonates can be catastrophic. For some neonates with severe congenital heart disease, the left ventricle is unable to pump sufficient blood to the body to support life. For these neonates, the right ventricle must take on the role of the non-functioning left ventricle, pumping partially oxygenated blood directly to the systemic circulation across the patent ductus arteriosus. This right-to-left shunting of blood depends on persistently high pulmonary vascular resistance, which creates the pressure differential that allows for the partially oxygenated blood to flow from the right ventricle into the aorta. Without this pulmonary vasoconstriction and resultant pulmonary hypertension, the right ventricle of these neonates would be unable to pump sufficient oxygenated blood through the body. Thus, if the pulmonary vascular resistance drops or is lowered, as would occur if iNO were administered, these neonates would be at very high risk of low blood pressure, low cardiac output, severe acidosis, cardiogenic shock, and sudden death. It is for this reason that when first approved, INOmax® was contraindicated for neonates that were right-to-left shunt dependent, or RTL-Dependent neonates. (Ex. 2, 2000 INOmax® Label at 4.)

8. When initially approved, INOmax® was not contraindicated in any other class of neonates, which was consistent with the clinical studies submitted to support the original FDA approval. These studies, referred to as the NINOS and CINRGI studies, administered iNO to

pediatric patients, including neonates. (Ex. 3, Neonatal Group; Ex. 4, Clark 2000.) Notably, neither of these studies excluded pediatric patients with left ventricular dysfunction ("LVD"). (Ex. 3, Neonatal Group at 598 (describing subject inclusion/exclusion criteria); Ex. 4, Clark 2000 at 469-70 (describing subject inclusion/exclusion criteria).)

9. In 2004, Plaintiff INO Therapeutics LLC ("INOT") sponsored a clinical trial known as the INOT22 study that compared the use and side effects of oxygen, iNO, and a combination of oxygen and iNO for determining pulmonary reactivity. (Ex. 1, the '966 patent at 9:65-67.) The INOT22 protocol did not exclude pediatric patients with other types of LVD than those dependent on right-to-left shunting of blood ("RTL-Dependent"). (*Id.* at 9:43-45; Ex. 5, Baldassare Decl. I, at ¶¶ 9,11; Ex. 6, Baldassarre Decl. II, at ¶ 7.) The INOT22 study was designed by INOT and a committee of "internationally recognized experts" in pediatric heart and lung disease ("the INOT22 Steering Committee"). (Ex. 5, Baldassarre Decl. I, at ¶¶ 7-8; Ex. 6, Baldassarre Decl. II, at ¶ 8.) Before the INOT22 study began, the protocol was carefully reviewed by more than 115 individuals "experienced in and responsible for the review of clinical trial protocols for patients safety"—including institutional review boards, independent ethics committees, the FDA, and equivalent international regulatory agencies. (Ex. 6, Baldassarre Decl. II, at ¶ 11.) Not one suggested that iNO might increase the likelihood of adverse events in pediatric patients with non-RTL-Dependent LVD. (*Id*.) Therefore, prior to initiating the original INOT22 protocol, the relationship between LVD and serious adverse events was not apparent to persons at multiple institutions whose charge it was to protect human subjects, and particularly pediatric patients, from inclusion in research that would subject them to known risks that were not disclosed. (Ex. 1, '966 patent at 9:31-40; Ex. 5, Baldassarre Decl. I, at ¶ 11; Ex. 6, Baldassarre Decl. II, at ¶ 11.)

10. After initiation and enrollment of the first 24 subjects in the INOT22 study, five serious adverse events ("SAEs") were observed including pulmonary edema, cardiac arrest, and hypotension. (Ex. 1, '966 patent at 12:26-13:2; Ex. 5, Baldassarre Decl. I, at ¶ 12.) In fact, at least, one infant died during the INOT22 study using the original protocol. (Ex. 1, '966 patent, at 12:26-13:2.)

11. "[A]fter the surprising and unexpected identification of SAEs in the early tested patients" the study was halted, and the INOT22 Steering Committee convened to review the unexpected SAEs. As a result, "it was determined that patients with pre-existing LVD had an increased risk of experiencing an [adverse event] or SAE upon administration. (Ex. 1, '966 patent at 12:26-31; Ex. 5, Baldassarre Decl. I, at ¶¶ 12-13.)

12. The protocol of the INOT22 study was then "amended to exclude patients with a baseline [Pulmonary Capillary Wedge Pressure ("PCWP")] greater than 20 mmHg," which was selected "to avoid enrollment of a pediatric population with LVD." (Ex. 1, '966 patent at 12:26-38; 13:64-66; Ex. 5, Baldassarre Decl. I, at ¶ 13.) Following the protocol change, the number of SAEs was significantly reduced. (*Id.* at ¶ 14.) As noted above 5 SAEs were observed in the first 24 patients (before the exclusion of patients with PCWP greater than 20 mmHg) but only 2 SAEs were observed in the last 100 study patients (after the exclusion of such patients). (*Id.*)

13. Prior to the INOT22 study with the amended protocol, there was no convincing scientific evidence that demonstrated an association between use of nitric oxide in young infants with LVD and serious adverse events, such as pulmonary edema. Had those of skill in the art even suspected the risk of SAEs in pediatric patients with LVD, the INOT22 study would not have been conducted with its original protocol. In fact, as Dr. Wessel stated in his declaration submitted during the prosecution of the '966 patent, he would have been "acting either

negligently or intentionally to harm babies, and [he] most certainly was not." (Ex. 7, Wessel Decl., at ¶ 8.)

14. Therefore, prior to INOT22, it was not routine, conventional, or well-understood to consider excluding pediatric patients with LVD from iNO treatment. After INOT22, experimental evidence in humans strongly supported the careful consideration of exclusion of pediatric subjects with LVD from treatment with inhaled nitric oxide.

15. As a result of the INOT22 study, the prescribing information for INOmax® now includes (i) a statement in the Warnings and Precautions section that states "Heart Failure: In patients with pre-existing left ventricular dysfunction, INOmax may increase pulmonary capillary wedge pressure leading to pulmonary edema," and (ii) new section 5.4 which includes the statement that "[i]n patients with pre-existing left ventricular dysfunction, INOmax may increase pulmonary capillary wedge pressure leading to pulmonary edema." (Ex. 8, Current INOmax® Label at 1, 3.)

16. The interactions between iNO and a child's circulatory and respiratory systems are complex and not fully understood. As noted by Evans (2016), "iNO is associated with a wide range of response in terms of improvement in oxygenation. At one end of the spectrum, there is no (or muted) change; at the other end, a baby will go from 100% oxygen to [room] air in a matter of minutes." (Ex. 9, Evans 2016.) Thus, some patients do not respond to iNO therapy, and such non-responsiveness demonstrates that there is no automatic correlation between iNO treatment and patient response.

17. Even when clinical circumstances suggest common mechanisms for hypoxic respiratory failure, response to iNO may be inexplicably different. For example, one cause of hypoxic respiratory failure is lung hypoplasia. Two common causes of lung hypoplasia are

oligohydramnios (a condition with low volumes of amniotic fluid in utero that is associated with low fetal lung volumes) and congenital diaphragmatic hernia (in which abdominal organs lie in the chest, causing mechanical compression and low fetal lung volumes). Response to iNO is different in these two conditions that are each associated with lung hypoplasia/low volumes.

18. De Waal and colleagues (2015) describe the favorable response to iNO when used in preterm babies with hypoxic respiratory failure attributable to small lungs caused by oligohydramnios. (Ex. 10, De Waal 2015.) But among babies with small lungs due to congenital diaphragmatic hernia, response to iNO is considerably less favorable. (Ex. 11, NINOS 1997.) Even among term and near-term neonates with hypoxic respiratory failure, the determinants of clinical response to iNO are not completely understood.

19. Furthermore, not every child with LVD, if treated with iNO, will be at risk for pulmonary edema, or for any other specific adverse event reported sporadically with the administration of iNO. Empirical evidence supporting this can be derived directly from the INOT22 study. In INOT22, "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." (Ex. 5, Baldassarre Decl. I at ¶ 14.)

20. As explained above, the difference in the SAE rates among those with and without pre-existing LVD in the INOT22 study was both dramatic and surprising and allowed for the improved methods disclosed in the patents. But the relationship between exposure to iNO and development of SAEs among those with LVD is not deterministic. Half of the iNO-exposed subjects with LVD suffered no serious adverse events, and conversely, 4% of those iNO-exposed subjects without LVD did suffer SAEs. (*Id.*)

21. The lack of a deterministic relationship between iNO and any particular adverse event in the presence of LVD is understandable given: a.) the complex local actions of nitric oxide, nitrogen dioxide, and oxygen (which are necessarily co-administered in varying concentrations in each subject receiving iNO), b.) the complex physiologies that constitute LVD, and c.) the complex homeostatic, biological systems in place to protect against physiological purturbations so severe as to be categorized as SAEs.

22. One of the SAEs observed in the INOT22 study, pulmonary edema, serves as an example. Pulmonary edema describes the condition in which there is excessive fluid in the spaces between the cells comprising the lung tissue (the interstitium), often spilling over into the alveolar spaces and interfering with gas exchange. Many factors influence the net movement of fluid from the vascular space into the interstitium. These include the hydrostatic pressures in the arterioles, venules, and interstitium; the airway pressure; the oncotic pressures in the vascular space and interstitium; and the permeability of the small blood vessels of the lungs.

23. The sum of these forces normally favor the net movement of fluid from the vascular space into the interstitium of the lung. The lymphatic system is designed to scavenge the extra fluid to prevent accumulation of pulmonary edema. Removal of interstitial fluid by the lymphatics protects each of us from developing pulmonary edema. Lymphatic dysfunction alone is a well-known cause of pulmonary edema.

24. When pulmonary edema occurs following iNO administration to children with pre-existing LVD, it results from a confluence of complex interactions between (at least) hydrostatic pressures, oncotic pressures, airway pressures, chemical effects on vascular permeability, lymphatic function, and pharmacological effects of iNO.

25. In fact, iNO may be an appropriate treatment to effectively treat LVD in certain pediatric patients. For example, patients with primary pulmonary hypertension, where the pressure in the right ventricle is elevated, have a shift in the interventricular septum causing an encroachment on the left ventricle. Because of this encroachment, the left ventricle has decreased early filling and a lower volume of blood to eject, resulting in LVD. Relieving the elevated pressure in the right ventricle will treat the LVD in these patients. iNO is an appropriate treatment for alleviating elevated pressure in the right ventricle for certain patients and thus may be effective in treating LVD in patients with primary pulmonary hypertension. Indeed, in my personal experience as a pediatric cardiologist, I have used iNO to treat patients with pulmonary hypertension and resultant LVD, and have observed that iNO improved left ventricular function in these patients by reducing the right ventricular pressure. In treating these patients with pulmonary hypertension and resultant LVD with iNO, I have not observed any SAEs following treatment with iNO.

26. A law of nature is a concise and precise description of a phenomenon in the natural world, such as Einstein's formula that $E=mc^2$ and Newton's law of gravity. Examples of laws of nature that apply in cardiovascular physiology include the Law of Laplace describing surface tension and wall tension, and Poiseuille's Law describing flow rate as a function of pressure drop, tube length and radius, and fluid viscosity. Laws of nature are revealed through the scientific method, and once identified, become tools of discovery and invention in science, technology, and engineering. For all the reasons discussed above, it is not a law of nature that treatment of a particular patient within the scope of the claims who has LVD with iNO necessarily results in pulmonary edema or another SAE, because there is no certain relationship

between LVD and efficacy or risk of SAE from iNO treatment in any individual pediatric patient.

G Rosenthal 1/27/2016

Geoffrey L. Rosenthal, M.D., Ph.D. Date

EXHIBIT 1

TO THE DECLARATION OF GEOFFREY L. ROSENTHAL, M.D. PH.D.

US008282966B2

(12) **United States Patent**
Baldassarre et al.

(10) **Patent No.: US 8,282,966 B2**
(45) **Date of Patent: *Oct. 9, 2012**

(54) **METHODS OF REDUCING THE RISK OF OCCURRENCE OF PULMONARY EDEMA IN CHILDREN IN NEED OF TREATMENT WITH INHALED NITRIC OXIDE**

(75) Inventors: **James S. Baldassarre**, Doylestown, PA (US); **Ralf Rosskamp**, Chester, NJ (US)

(73) Assignee: **INO Therapeutics LLC**, Hampton, NJ (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **12/821,020**

(22) Filed: **Jun. 22, 2010**

(65) **Prior Publication Data**

US 2010/0330207 A1 Dec. 30, 2010

Related U.S. Application Data

(63) Continuation of application No. 12/494,598, filed on Jun. 30, 2009, now abandoned.

(51) **Int. Cl.**

A01N 59/00	(2006.01)
A61K 33/00	(2006.01)
C01B 21/24	(2006.01)
A61M 16/00	(2006.01)

(52) **U.S. Cl.** **424/718**; 128/200.24; 423/405

(58) **Field of Classification Search** ..... None
See application file for complete search history.

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Primary Examiner — Ernst Arnold
(74) *Attorney, Agent, or Firm* — Fish & Richardson P.C.

(57) **ABSTRACT**

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

29 Claims, No Drawings

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METHODS OF REDUCING THE RISK OF OCCURRENCE OF PULMONARY EDEMA IN CHILDREN IN NEED OF TREATMENT WITH INHALED NITRIC OXIDE

CROSS REFERENCE TO RELATED APPLICATIONS

This application claims priority to U.S. patent application Ser. No. 12/494,598, entitled "Methods of Treating Term and Near-Term Neonates Having Hypoxic Respiratory Failure Associated with Clinical or Echocardiographic Evidence of Pulmonary Hypertension", filed on Jun. 30, 2009, incorporated herein by reference.

BACKGROUND OF THE INVENTION

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.

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 R G et al., 1983, Acute Hemodynamic Effects of Nitroglycerin in Pulmonary Hypertension, *American College of Physicians* 99:9-13; Ajami G H 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 J J 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 J W 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

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.

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.

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.

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.

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.

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

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.

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.

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

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

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.

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

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

In another exemplary embodiment of the method, the patients who have pre-existing LVD are at risk of experiencing and increased rate of one or more AEs or SAEs selected

from pulmonary edema, hypotension, cardiac arrest, electrocardiogram changes, hypoxemia, hypoxia, bradycardia or associations thereof.

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.

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

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

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 U.S. Pat. Nos. 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; U.S. patent application Ser. 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.

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.

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

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

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

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

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

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.

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

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

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

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

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.

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.

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 L J, Kerr K M, Pulmonary Hypertension, in *Critical Care Medicine: Principles of Diagnosis and Management in the Adult,* 2d *Ed.*, Parillo J E, Dellinger R P (eds.), Mosby, Inc. 2001, pp. 900-09 at 906;

Kinsella J P, Abman S H, 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 D F (ed.), NICU Ink Book Publishers, 1997, pp. 369-378 at 372-73).

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.

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

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).

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

TABLE 1

Summary of Clinical Results from CINRGI Study

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

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

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

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

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.

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 AE of treatment on the need for rehospitalization, special medical services, pulmonary disease, or neurological squeal.

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.

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%)

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.

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

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

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.

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

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.

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 · 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)

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

TABLE 5-continued

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

Ratio PVRI/SVRI	Treatment: NO Plus O_2 (n = 108)	O_2 (n = 105)	NO (n = 106)
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)

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)

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

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

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.

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.

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.

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.

SAEs were collected from the start of study treatment until hospital discharge or 12 hours, whichever occurred sooner. Three SAEs were reported during the study period, and a total of 7 SAEs were reported. Three of these were fatal SAEs and 4 were nonfatal (one of which led to study discontinuation). In addition, one non-serious AE also lead to discontinuation. A list of subjects who died, discontinued or experienced an SAE is provided in Table 5 below.

TABLE 5

Subjects that died, discontinued or experienced SAEs

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

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 C S et al., 1996, Inhaled Nitric Oxide in Cardiac Failure: Vascular Versus Ventricular Effects, *J Cardiovascular Pharmacology* 27:80-85; Bocchi E A et al., 1994, Inhaled Nitric Oxide Leading to Pulmonary Edema in Stable Severe Heart Failure, *Am J Cardiology* 74:70-72; and, Semigran M J et al., 1994, Hemodynamic Effects of Inhaled Nitric Oxide in Heart Failure, *J Am Coll Cardiology* 24:982-988).

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 E A et al., 1994; Semigran M J et al., 1994).

In the INOT22 study, 10 of the total 134 patients had a baseline PCWP≧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.

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.

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

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 C J 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.

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 reducing the risk of occurrence of pulmonary edema associated with a medical treatment comprising inhalation of 20 ppm nitric oxide gas, said method comprising:

(a) performing echocardiography to identify a child in need of 20 ppm inhaled nitric oxide treatment for pulmonary hypertension, wherein the child is not dependent on right-to-left shunting of blood;

(b) determining that the child identified in (a) has a pulmonary capillary wedge pressure greater than or equal to 20 mm Hg and thus has left ventricular dysfunction, so is at particular risk of pulmonary edema upon treatment with inhaled nitric oxide; and

(c) excluding the child from inhaled nitric oxide treatment based on the determination that the child has left ventricular dysfunction and so is at particular risk of pulmonary edema upon treatment with inhaled nitric oxide.

2. The method of claim **1**, wherein the child is a neonate.

3. The method of claim **1**, wherein step (b) comprises measuring the child's pulmonary capillary wedge pressure.

4. The method of claim **1**, wherein the child's left ventricular dysfunction is attributable to congenital heart disease.

5. The method of claim **1**, wherein the child is determined to be at particular risk not only of pulmonary edema, but also of other Serious Adverse Events, upon treatment with inhaled nitric oxide, and the child is excluded from inhaled nitric oxide treatment based on the determination that the child has left ventricular dysfunction and so is at particular risk not only of pulmonary edema, but also of other Serious Adverse Events, upon treatment with inhaled nitric oxide.

6. A method of reducing the risk of occurrence of pulmonary edema associated with a medical treatment comprising inhalation of 20 ppm nitric oxide gas, said method comprising:

(a) carrying out a diagnostic process comprising measuring blood oxygen level, to identify a child as being in need of 20 ppm inhaled nitric oxide treatment for hypoxic respiratory failure, wherein the child is not dependent on right-to-left shunting of blood;

(b) determine determining that the child has a pulmonary capillary wedge pressure greater than or equal to 20 mm Hg and thus has left ventricular dysfunction, so is at particular risk of pulmonary edema upon treatment with inhaled nitric oxide; and

(c) excluding the child from treatment with inhaled nitric oxide based on the determination that the child has left ventricular dysfunction and so is at particular risk of pulmonary edema upon treatment with inhaled nitric oxide.

7. The method of claim **6**, wherein the diagnostic process of step (a) further comprises performing echocardiography.

8. The method of claim **6**, wherein the child is a neonate.

9. The method of claim **6**, wherein step (b) comprises measuring the child's pulmonary capillary wedge pressure.

10. The method of claim **6**, wherein the left ventricular dysfunction is attributable to congenital heart disease.

11. The method of claim **6**, wherein the child is determined to be at particular risk not only of pulmonary edema, but also of other Serious Adverse Events, upon treatment with inhaled nitric oxide, and the child is excluded from inhaled nitric oxide treatment based on the determination that the child has left ventricular dysfunction and so is at particular risk not only

of pulmonary edema, but also other Serious Adverse Events, upon treatment with inhaled nitric oxide.

12. The method of claim **11**, wherein the left ventricular dysfunction is attributable to congenital heart disease.

13. A method of treatment comprising:

(a) performing echocardiography to identify a plurality of children who are in need of 20 ppm inhaled nitric oxide treatment for pulmonary hypertension, wherein the children are not dependent on right-to-left shunting of blood;

(b) determining that a first child of the plurality has a pulmonary capillary wedge pressure greater than or equal to 20 mm Hg and thus has left ventricular dysfunction, so is at particular risk of pulmonary edema upon treatment with inhaled nitric oxide;

(c) determining that a second child of the plurality does not have left ventricular dysfunction;

(d) administering the 20 ppm inhaled nitric oxide treatment to the second child; and

(e) excluding the first child from treatment with inhaled nitric oxide, based on the determination that the first child has left ventricular dysfunction, so is at particular risk of pulmonary edema upon treatment with inhaled nitric oxide.

14. The method of claim **13**, wherein step (a) further comprises measuring blood oxygen levels in the first and second children and thereby determining that the first and second children are hypoxic.

15. The method of claim **13**, wherein the second child has congenital heart disease.

16. The method of claim **13**, wherein step (b) comprises measuring the first child's pulmonary capillary wedge pressure.

17. The method of claim **13**, wherein determining that the second child of the plurality does not have pre-existing left ventricular dysfunction comprises performing echocardiography.

18. The method of claim **13**, wherein the left ventricular dysfunction is attributable to congenital heart disease.

19. The method of claim **13**, wherein the left ventricular dysfunction of the first child is attributable to congenital heart disease.

20. The method of claim **13**, wherein the first child is determined to be at particular risk not only of pulmonary edema, but also of other Serious Adverse Events, upon treatment with inhaled nitric oxide, and the first child is excluded from inhaled nitric oxide treatment based on the determination that the first child has left ventricular dysfunction and so is at particular risk not only of pulmonary edema, but also other Serious Adverse Events, upon treatment with inhaled nitric oxide.

21. The method of claim **20**, wherein the pre-existing left ventricular dysfunction of the first child is attributable to congenital heart disease.

22. A method of treatment comprising:

(a) identifying a plurality of children who are in need of 20 ppm inhaled nitric oxide treatment, wherein the children are not dependent on right-to-left shunting of blood;

(b) in the first child of the plurality, measuring pulmonary capillary wedge pressure to determine that the 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) in the second child of the plurality, performing echocardiography and/or measurement of pulmonary capillary wedge pressure to determine that the 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.

23. The method of claim **22**, wherein step (a) comprises performing echocardiography to determine that the first and second children have pulmonary hypertension.

24. The method of claim **22**, wherein step (a) comprises measuring blood oxygen levels in the first and second children and thereby determining that the first and second children are hypoxic.

25. The method of claim **22**, wherein the second child has congenital heart disease.

26. The method of claim **22**, wherein the left ventricular dysfunction is attributable to congenital heart disease.

27. The method of claim **22**, wherein the pre-existing left ventricular dysfunction of the first child is attributable to congenital heart disease.

28. The method of claim **22**, wherein the first child is determined to be at particular risk not only of pulmonary edema, but also of other Serious Adverse Events, upon treatment with inhaled nitric oxide, and the first child is excluded from inhaled nitric oxide treatment based on the determination that the first child has pre-existing left ventricular dysfunction and so is at particular risk not only of pulmonary edema, but also other Serious Adverse Events, upon treatment with inhaled nitric oxide.

29. The method of claim **28**, wherein the pre-existing left ventricular dysfunction of the first child is attributable to congenital heart disease.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 8,282,966 B2
APPLICATION NO. : 12/821020
DATED : October 9, 2012
INVENTOR(S) : James S. Baldassarre

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Title Page 1, Column 2, item [56] (OTHER PUBLICATIONS), line 6:

After "638)" insert -- . --.

Title Page 1, Column 2, item [56] (OTHER PUBLICATIONS), lines 8-9:

Delete "Bocchi the American Journal of Cardiology 1994, 74, pp.70-72. 4 pages)." and insert therefor -- Bocchi et al., (The American Journal of Cardiology 1994, 74, pp. 70-72). 4 pages. --.

Title Page 1, Column 2, item [56] (OTHER PUBLICATIONS), line 14:

Delete "(Achives" and insert -- (Archives -- therefor.

Title Page 1, Column 2, item [56] (OTHER PUBLICATIONS), line 14:

Delete "F47-F49." and insert -- F47-F49). -- therefor.

Title Page 1, Column 2, item [56] (OTHER PUBLICATIONS), lines 24-25:

Delete "Bocchi et al. The American Journal of Cardiology 1994, 74, pp:70-72. 4 pages).".

Title Page 1, Column 2, item [56] (OTHER PUBLICATIONS), line 36:

Delete "Adatia et al," and insert -- Adatia et al., -- therefor.

Title Page 1, right column, item [56] (OTHER PUBLICATIONS), line 37:

Delete "Hyptertension" and insert -- Hypertension -- therefor.

Signed and Sealed this
Sixteenth Day of April, 2013

Teresa Stanek Rea
Acting Director of the United States Patent and Trademark Office

Title Page 1, right column, item [56] (OTHER PUBLICATIONS), lines 42-45:

Delete "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, 1998, vol. 115, pp. 700-704." and insert the same as a new entry beginning at page 1, right column, line 43.

Title Page 1, right column, item [56] (OTHER PUBLICATIONS), line 55:

Delete "Hypertemsion:" and insert -- Hypertension -- therefor.

Title Page 1, right column, item [56] (OTHER PUBLICATIONS), line 59:

Delete "dysfuction" and insert -- dysfunction -- therefor.

In the Specifications:

Column 12, line 6:

Delete "Table 5" and insert -- Table 7 -- therefor.

Column 12, line 46:

Delete "Table 5" and insert -- Table 7 -- therefor.

Column 12, line 48:

Delete the table heading "TABLE 5" and insert -- TABLE 7 -- therefor.

In the Claims:

Column 14, Claim 6, line 45:

Delete "determine".

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 8,282,966 B2
APPLICATION NO. : 12/821020
DATED : October 9, 2012
INVENTOR(S) : James S. Baldassarre

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In the Specifications:

Column 12, line 46:

Delete "Table 5" and insert -- Table 7 -- therefor.

Signed and Sealed this
Thirtieth Day of April, 2013

Teresa Stanek Rea
Acting Director of the United States Patent and Trademark Office

EXHIBIT 2

TO THE DECLARATION OF GEOFFREY L. ROSENTHAL, M.D. PH.D.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20845

FINAL PRINTED LABELING

INOmaxTM (nitric oxide) for inhalation

100 and 800ppm (parts per million)

DESCRIPTION

INOmaxTM (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 (0.8%) and nitrogen (99.2%). 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.

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

Figure 1

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**.)

(i) 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 if 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[a,b]	77 (64%)	52 (46%)	0.006
Death	20 (17%)	16 (14%)	0.60
ECMO	66 (55%)	44 (39%)	0.014

[a] Extra-corporeal membrane oxygenation

[b] 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 PaO2 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. Inhalednitric 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 performedat 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 theirmental, motor, audiologic, or neurologic evaluations.

(ii) 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 PaO2 >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[a,b]	51/89 (57%)	30/97 (31%)	< 0.001
Death	5/89 (6%)	3/97 (3%)	0.48

[a] Extra-corporeal membrane oxygenation

[b] 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 PaO2, 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.**)

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

Methemogloginemia 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, NO2 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 NO2 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. In particular, although there are no 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. INOmax has been administered with tolazoline, dopamine, dobutamine, steroids, surfactant, and high-frequency ventilation.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No long-term studies in animals to evaluate the carcinogenic potential of nitric oxide have been performed. 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 or harm to the developing fetus.

Pregnancy: Category C

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

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.

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.

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, 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

Averse Event	Placebo (n=89)	Inhaled NO (n=97)
Hypotension	9 *(10%)*	13 *(13%)*
Withdrawal syndrome	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%)*
Cellulitis	0 *(0%)*	5 *(5%)*

Stridor	3 *(3%)*	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.

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 who 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 STUDIES).

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. This 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 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, Inc

54 Old Highway 22

Clinton, NJ 08809 USA

EXHIBIT 3

TO THE DECLARATION OF GEOFFREY L. ROSENTHAL, M.D. PH.D.

The New England Journal of Medicine

VOLUME 336 FEBRUARY 27, 1997 NUMBER 9

INHALED NITRIC OXIDE IN FULL-TERM AND NEARLY FULL-TERM INFANTS WITH HYPOXIC RESPIRATORY FAILURE

THE NEONATAL INHALED NITRIC OXIDE STUDY GROUP*

ABSTRACT

Background Neonates with pulmonary hypertension have been treated with inhaled nitric oxide because of studies suggesting that it is a selective pulmonary vasodilator. We conducted a randomized, multicenter, controlled trial to determine whether inhaled nitric oxide would reduce mortality or the initiation of extracorporeal membrane oxygenation in infants with hypoxic respiratory failure.

Methods Infants born after a gestation of ≥34 weeks who were 14 days old or less, had no structural heart disease, and required assisted ventilation and whose oxygenation index was 25 or higher on two measurements were eligible for the study. The infants were randomly assigned to receive nitric oxide at a concentration of 20 ppm or 100 percent oxygen (as a control). Infants whose partial pressure of arterial oxygen (PaO_2) increased by 20 mm Hg or less after 30 minutes were studied for a response to 80-ppm nitric oxide or control gas.

Results The 121 infants in the control group and the 114 in the nitric oxide group had similar base-line clinical characteristics. Sixty-four percent of the control group and 46 percent of the nitric oxide group died within 120 days or were treated with extracorporeal membrane oxygenation ($P=0.006$). Seventeen percent of the control group and 14 percent of the nitric oxide group died (P not significant), but significantly fewer in the nitric oxide group received extracorporeal membrane oxygenation (39 percent vs. 54 percent, $P=0.014$). The nitric oxide group had significantly greater improvement in PaO_2 (mean [±SD] increase, 58.2±85.2 mm Hg, vs. 9.7±51.7 mm Hg in the controls; $P<0.001$) and in the oxygenation index (a decrease of 14.1±21.1, vs. an increase of 0.8±21.1 in the controls; $P<0.001$). The study gas was not discontinued in any infant because of toxicity.

Conclusions Nitric oxide therapy reduced the use of extracorporeal membrane oxygenation, but had no apparent effect on mortality, in critically ill infants with hypoxic respiratory failure. (N Engl J Med 1997; 336:597-604.)

HYPOXIC respiratory failure in neonates born at or near term (at ≥34 weeks' gestation) may be caused by conditions such as primary persistent pulmonary hypertension, respiratory distress syndrome, aspiration of meconium, pneumonia or sepsis, and congenital diaphragmatic hernia.[1,2] Conventional therapy, short of extracorporeal membrane oxygenation, involves support with oxygen, mechanical ventilation, and the induction of alkalosis, neuromuscular blockade, and sedation.[3-6] None of these therapies have been found to reduce mortality or the need for extracorporeal membrane oxygenation. To date, selective pulmonary vasodilators free of systemic side effects have not been studied in large trials of neonates.[7]

Nitric oxide, or endothelium-derived relaxing factor, is important in regulating vascular muscle tone.[8-13] In newborn lambs with pulmonary hypertension induced by hypoxia, the inhalation of 40 to 80 parts per million (ppm) of nitric oxide reversed pulmonary vasoconstriction without affecting the systemic circulation.[14-16] Two recent studies of neonates with severe persistent pulmonary hypertension have shown that inhaled nitric oxide rapidly improved preductal oxygen saturation, without detectable toxic effects.[17,18] A prospective study of multiple randomized doses of inhaled nitric oxide in infants referred for extracorporeal membrane oxygenation did not find a correlation between the dose of nitric oxide and the degree of improvement in oxygenation.[19] We conducted a prospective, multicenter, randomized, controlled, double-blind trial to evaluate whether inhaled

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nitric oxide would reduce mortality or the need for extracorporeal membrane oxygenation in infants born at or near term who had hypoxic respiratory failure that was unresponsive to aggressive conventional therapy.

METHODS

Study Hypotheses

The primary hypothesis in the study was that administering inhaled nitric oxide to infants born at 34 or more weeks of gestation who had hypoxic respiratory failure and an oxygenation index of 25 or higher would reduce the risk of death by day 120 or the initiation of extracorporeal membrane oxygenation from 50 percent in control infants to 30 percent in infants given nitric oxide, a relative reduction of 40 percent. The oxygenation index was calculated as the mean airway pressure times the fraction of inspired oxygen (FiO_2) divided by the partial pressure of arterial oxygen (PaO_2) times 100.

The secondary hypothesis was that 30 minutes after the start of treatment, inhaled nitric oxide would increase PaO_2 and decrease the oxygenation index and the alveolar–arterial oxygen gradient. We hypothesized that among the surviving infants, treatment with inhaled nitric oxide would shorten hospitalization without increasing the duration of assisted ventilation or the incidence of air leakage, bronchopulmonary dysplasia, or neurodevelopmental disability at 18 to 24 months.

Study Patients

Infants born at 34 or more weeks of gestation who required assisted ventilation for hypoxic respiratory failure and had an oxygenation index of at least 25 on two measurements made at least 15 minutes apart were eligible for the trial. Hypoxic respiratory failure was caused by persistent pulmonary hypertension, meconium aspiration, pneumonia or sepsis, respiratory distress syndrome, or suspected pulmonary hypoplasia associated with oligohydramnios and premature rupture of the membranes. All the infants were required to have an indwelling catheter and to undergo echocardiography before randomization. Echocardiographic evidence of pulmonary hypertension was not required, because studies have shown that inhaled nitric oxide improves the matching of ventilation with perfusion and may reduce intrapulmonary shunting in the absence of a direct intracardiac shunt.[20,21]

Infants were considered ineligible for the study if they were more than 14 days old, had a congenital diaphragmatic hernia, or were known to have congenital heart disease, or if it had been decided not to provide full treatment. The study centers attempted to obtain a cranial ultrasonogram before enrolling an infant in the study. Consent was obtained from the parents or guardians before the infants underwent randomization, and each study center obtained approval from the institutional review board before enrollment began. Copies of the study protocol are available from the authors on request.

Guidelines for Management

The approach to care before enrollment was not specified by the study protocol. Each participating center developed general management guidelines to be used throughout the study and agreed to use the most aggressive forms of conventional therapy before randomization. These guidelines included the maintenance of a mean arterial blood pressure above 45 mm Hg, the induction of alkalosis (range of target pH, 7.45 to 7.6), and treatment with bovine surfactant (BLES, BLES Biochemicals, London, Ont., Canada; or Survanta, Abbott Laboratories, Columbus, Ohio) before the start of treatment with the study gas. The protocol specified that the mode of ventilation (conventional or high frequency) could not be changed after randomization, except as part of weaning from assisted ventilation.

Randomization

The infants were stratified according to study center and randomly assigned by telephone to receive either 100 percent oxygen (the control treatment) or nitric oxide according to a permuted-block design developed and implemented by the coordinating center.

Administration and Monitoring of Study Gas

If treatment with the study gas could be started within 15 minutes after the second qualifying oxygenation-index score was obtained, the arterial-blood gas values from that measurement served as the base-line values in assessing the response to the study treatment. If the treatment could not be started within the 15-minute period, a third measurement of arterial-blood gas, obtained before the administration of the study gas, was used to determine the base-line value. Primary-grade nitric oxide was supplied in a concentration of 800 ppm in balanced nitrogen (Canadian Liquid Air, Montreal; and Ohmeda, Liberty Corner, N.J.); the gas was certified to be within ±1 percent of the stated nitric oxide content and to contain less than 5 ppm of nitrogen dioxide. The gas mixture was sampled after it entered the injection site of the inspiratory circuit and before it reached the infant's endotracheal tube and was analyzed continuously for nitric oxide and nitrogen dioxide with chemiluminescence (model 42H, Thermo Environmental Instruments, Franklin, Mass.; and model CLD 700AL, ECO Physics, Durten, Switzerland) or with electrochemical analyzers (Pulmonox II, Pulmonox, Tolfield, Alta., Canada; and Dräger Prac II, Dräger, Chantilly, Va.). Quality-control procedures ensured accurate calibration and prevented the supply tank of nitric oxide gas from being contaminated.

Except when the treatment was initiated and when the concentration of the study gas was changed, the infants were cared for by clinical teams unaware of each infant's treatment assignment; the randomization was performed, the gas administered, and safety monitored by designated persons who were not involved in the clinical care. Levels of inspired oxygen, nitric oxide, and nitrogen dioxide were recorded every two hours and after the settings of the ventilator were changed. We kept the clinical teams unaware of the treatment assignments by making mock adjustments in the case of the control infants, covering the analyzer readings and the gas tanks, and sampling the supply of oxygen before the injection site of the study gas.

A response to treatment was defined according to the change from base line in the PaO_2 30 minutes after the initial exposure to the study gas (a complete response was defined as an increase of more than 20 mm Hg; a partial response, as an increase of 10 to 20 mm Hg; and no response, as an increase of less than 10 mm Hg) when the two measurements were made at comparable sampling sites. When an infant had a complete response, treatment with the study gas (either nitric oxide at a concentration of 20 ppm or 100 percent oxygen) was continued. When an infant had less than a complete response, the treatment was stopped for 15 minutes if the stoppage was tolerated, the arterial-blood gases were measured again, and then the study gas was administered at a maximal concentration of 80 ppm. Arterial-blood gases were measured again 30 minutes later. Infants who had complete responses to the maximal concentration continued to be treated at that concentration; in infants with partial responses, treatment was continued at the lowest concentration of gas that produced at least a partial response. If an infant had no response with either the 20-ppm or the 80-ppm concentration of gas, treatment was discontinued. Gas was also discontinued in any infant whose condition deteriorated (absolute decrease in oxygen saturation, >10 percent) before the end of the initial phase of administration at either the high or the low concentration, and such infants were classified as having no response. When an infant did not respond to the initial administration of the study gas, the treatment could be attempted again as many as three times at six-hour intervals. No crossover between study groups was allowed.

If an infant continued to receive the study gas after the initial

dosing algorithm, the gas was monitored in an unmasked fashion by designated persons who were not involved with the infant's clinical care. The protocol suggested algorithms for weaning infants from the study gas, escalating the dose of gas after the occurrence of clinical deterioration, and starting treatment again after successful weaning. The study protocol permitted treatment with the study gas for a cumulative maximum of 336 hours (14 days). Decisions about initiating extracorporeal membrane oxygenation were made by the blinded clinical team on the basis of center-specific criteria.

Monitoring of Safety

Blood methemoglobin concentrations were measured 1, 3, 6, and 12 hours after the start of treatment with the study gas and every 12 hours thereafter until 24 hours after the treatment ended. Methemoglobin levels of 5 to 10 percent were managed by reducing the concentration of study gas by half until the level fell below 5 percent. The study gas was discontinued if the methemoglobin level exceeded 10 percent. If the concentration of nitrogen dioxide exceeded 7 ppm, the study gas was discontinued; the gas was decreased by half if the concentration was 5 to 7 ppm.

The infants were monitored for signs of bleeding. Cranial ultrasonography was performed before randomization and 24 hours after the final discontinuation of the study gas. All the readings were done by local ultrasonographers.[22]

Statistical Analysis

According to the data from the participating centers, we estimated that mortality or the use of extracorporeal membrane oxygenation in infants with an oxygenation-index score between 25 and 40 would be 50 percent. To demonstrate a 40 percent reduction in the primary outcome with a power of 0.90 and a two-tailed alpha of 0.05, 125 patients were required in each group. The primary analysis was an intention-to-treat analysis.

Continuous variables were compared by t-tests or Wilcoxon tests, and discrete variables were compared by chi-square tests. The Gart test was used to evaluate the homogeneity of relative risks.[23]

The trial was monitored by an independent Data Safety and Monitoring Committee, which planned evaluations after approximately one third and two thirds of the study patients were enrolled. To reduce the overall probability of a type I error as much as possible, significance was tested at each interim analysis by the group-sequential method of Lan and DeMets with the O'Brien–Fleming spending function.[24] Results are presented as means ±SD.

RESULTS

The trial was terminated at the recommendation of the Data Safety and Monitoring Committee after the second planned review of data, which showed that the z value had crossed the predetermined boundary of statistical significance. After the recommendation was reviewed and accepted by the National Institute of Child Health and Human Development and the investigators, recruitment ceased on May 2, 1996.

Base-Line Characteristics

Two hundred thirty-five infants were enrolled in the trial. There were no significant differences between the study groups in the characteristics of the patients (Table 1), treatment methods, or status at the time of randomization (Table 2). Seventy-two percent of the controls and 71 percent of the treated infants received surfactant before randomization, and 50 percent and 49 percent, respectively, received it within six hours before randomization. High-frequency ventilation, primarily oscillatory, was used in 55 percent of both groups; 37 percent of the controls and 32 percent of the treated infants received such treatment at randomization. Over 90 percent of all the infants received volume support, vasopressor support, neuromuscular blockade, and sedation before randomization (Table 2).

TABLE 1. CHARACTERISTICS OF THE PATIENTS.*

CHARACTERISTIC	CONTROL GROUP (N=121)	NITRIC OXIDE GROUP (N=114)
Birth weight — g	3359±597	3460±578
Gestational age — wk	38.9±2.2	39.3±1.8
Male sex — no. (%)	76 (62.8)	63 (55.3)
Race — no. (%)†		
Black	19 (16.0)	19 (17.1)
White	72 (60.5)	70 (63.1)
Hispanic	17 (14.3)	13 (11.7)
Other	11 (9.2)	9 (8.1)
Not born in treating facility — no. (%)	93 (76.9)	92 (80.7)
Age at admission‡		
<12 hr	47 (50.5)	41 (45.1)
12–24 hr	20 (21.5)	20 (22.0)
>24 hr	26 (28.0)	30 (33.0)
1-Minute Apgar score <3 — no. (%)§	25 (20.8)	28 (24.8)
Primary diagnosis — no. (%)		
Persistent pulmonary hypertension of the newborn	22 (18.2)	19 (16.7)
Respiratory distress syndrome	15 (12.4)	10 (8.8)
Meconium aspiration syndrome	58 (47.9)	58 (50.9)
Pneumonia or sepsis	24 (19.8)	26 (22.8)
Other	2 (1.7)	1 (0.9)

*Plus–minus values are means ±SD.

†Data on race are based on 119 infants in the control group and 111 infants in the nitric oxide group.

‡Data for this variable are based on 93 infants in the control group and 91 infants in the nitric oxide group.

§Data for this variable are based on 120 infants in the control group and 113 infants in the nitric oxide group.

The causes of hypoxic respiratory failure are shown in Table 1. Forty-nine percent of all randomized infants had meconium aspiration syndrome; 17 percent had persistent pulmonary hypertension. Echocardiography was performed before randomization in 228 infants (97 percent); of the 226 infants for whom complete data were available, 78 percent had evidence of pulmonary hypertension (right-to-left or bidirectional shunting, tricuspid-valve regurgitation, or both). There was no difference in the prevalence of pulmonary hypertension between the study groups.

Randomization occurred 1.7±2.3 days after birth for the controls and 1.7±1.8 days after birth for the treated infants (Table 2). Data from the first qualifying arterial-blood gas measurement are also shown in Table 2; on the second qualifying measurement, the oxygenation index was 46.3±19.9 in the control

TABLE 2. TREATMENT VARIABLES AND STATUS OF THE PATIENTS AT RANDOMIZATION.*

VARIABLE	CONTROL GROUP (N=121)	NITRIC OXIDE GROUP (N=114)
Treatment — no. of patients (%)		
Volume support	116 (96.7)†	108 (94.7)
Vasopressor support	121 (100.0)	108 (94.7)
Tolazoline	16 (13.3)†	23 (20.2)
Sedation or analgesia	120 (99.2)	113 (99.1)
Neuromuscular blockade	115 (95.0)	107 (93.9)
Alkalosis	106 (87.6)	88 (77.2)
Surfactant	87 (71.9)	81 (71.1)
High-frequency ventilation	67 (55.4)	63 (55.3)
Air leaks — no. of patients (%)	25 (20.7)	20 (17.5)
Pulmonary hemorrhage — no. of patients (%)	22 (18.2)	18 (15.8)
First qualifying arterial-blood gas value		
Oxygenation index	45.1±22.4	43.0±17.6
Mean airway pressure (cm of water)	18.3±4.4	18.3±4.3
FiO_2 (mm Hg)	1.0±0.0	1.0±0.0
PaO_2 (mm Hg)	45.5±13.9	46.8±15.5
Alveolar–arterial oxygen gradient (mm Hg)	613.7±40.3	616.1±33.5
Age at randomization (days)	1.7±2.3	1.7±1.8
Median time, randomization to study-gas initiation (min)‡	10.0	15.0

*Plus–minus values are means ±SD. FiO_2 denotes fraction of inspired oxygen, and PaO_2 partial pressure of arterial oxygen.

†A total of 120 patients were studied for this variable.

‡Data for this variable are based on 117 infants in the control group and 113 in the nitric oxide group.

group and 47.3±31.3 in the nitric oxide group. Sixty-two percent of the control group and 64 percent of the nitric oxide group had a third arterial-blood gas measurement before treatment with the study gas was begun. The median time from randomization to the administration of the study gas was 10 minutes in the control group and 15 minutes in the nitric oxide group (Table 2). Five randomized infants (four in the control group and one in the nitric oxide group) did not receive study gas.

Primary Outcome

The incidence of the primary outcome (death by 120 days of age or the initiation of extracorporeal membrane oxygenation) was significantly lower in the nitric oxide group than in the control group (46 percent vs. 64 percent; relative risk, 0.72; 95 percent confidence interval, 0.57 to 0.91; P=0.006, a significant difference given the Lan–DeMets cutoff of 0.044) (Table 3). Thirty-six infants died, among whom 17 (9 in the control group and 8 in the nitric oxide group) received extracorporeal membrane oxygenation. Among the other 19 infants who died, 10 (5 in each group) had contraindications to extracorporeal membrane oxygenation; 5 (3 in the control group and 2 in the nitric oxide group) had their life support withdrawn; and 4 (3 and 1 in the respective groups) did not meet center-specific criteria for

TABLE 3. OUTCOMES OF ADMINISTRATION OF THE STUDY GAS, ACCORDING TO GROUP.*

OUTCOME	CONTROL GROUP (N=121)	NITRIC OXIDE GROUP (N=114)	P VALUE
Death by day 120 or ECMO — no. (%)	77 (63.6)	52 (45.6)	0.006
Death — no. (%)	20 (16.5)	16 (14.0)	0.60
ECMO — no. (%)	66 (54.5)	44 (38.6)	0.014
Change in PaO_2 — mm Hg	9.7±51.7	58.2±85.2	<0.001
Change in oxygenation index	0.8±21.1	−14.1±21.1	<0.001
Change in alveolar–arterial oxygen gradient — mm Hg	−6.7±57.5	−60.0±85.1	<0.001
Outcomes in surviving infants			
Length of hospitalization — days	29.5±22.6	36.4±44.8	0.17
Duration of assisted ventilation — days	11.7±13.0	11.6±7.0	0.97
Air leak after randomization — no. (%)	5 (5.1)	5 (5.2)	0.96
Bronchopulmonary dysplasia — no. (%)†	12 (11.9)	15 (15.3)	0.48

*Plus–minus values are means ±SD. ECMO denotes extracorporeal membrane oxygenation, and PaO_2 partial pressure of arterial oxygen.

†This condition was considered to be present when there was dependence on oxygen at the age of 28 days accompanied by abnormal results on chest radiography.

extracorporeal membrane oxygenation. There were no differences between the groups in the causes of death. The infants in the nitric oxide group received extracorporeal membrane oxygenation less often (39 percent) than the controls (55 percent, $P=0.014$) (Table 3). The median time from randomization to the initiation of extracorporeal membrane oxygenation was 4.4 hours in the control group and 6.7 hours in the nitric oxide group ($P=0.04$).

Secondary Outcomes

Among the surviving infants, there were no differences between the groups with respect to the length of hospitalization, the number of days of respiratory support (assisted ventilation, continuous positive airway pressure, or oxygen), or the incidence of air leakage or bronchopulmonary dysplasia (Table 3).

Thirty minutes after the administration of the study gas began, the infants in the nitric oxide group had a significantly greater mean increase in PaO_2 than the controls (58.2±85.2 vs. 9.7±51.7 mm Hg), a significantly greater change in the oxygenation index (a decrease of 14.1±21.1 as compared with an increase of 0.8±21.1), and a significantly greater decrease in the alveolar–arterial oxygen gradient (60.0±85.1 vs. 6.7±57.5 mm Hg; $P<0.001$ for all three comparisons) (Table 3).

More infants in the nitric oxide group than in the control group had at least a partial response to the initial administration of the study gas (66 percent vs. 26 percent, $P<0.001$) (Table 4). Of the 125 infants who had no response to 20-ppm nitric oxide or control gas, similar proportions of the nitric oxide group (18 percent [7 of 38]) and the control group (20 percent [17 of 87]) had at least partial responses to 80-ppm nitric oxide or control gas ($P=0.30$). Of the 30 infants who had partial responses to the study gas at 20 ppm, 29 percent of the nitric oxide group (5 of 17) and 8 percent of the control group (1 of 13) had at least a partial response at 80 ppm ($P=0.34$). Therefore, a majority of the infants who did not have complete responses at the 20-ppm concentration and who were evaluated at the 80-ppm concentration had no response to the study gas at the higher concentration (nitric oxide group, 77 percent [41 of 53]; control group, 81 percent [75 of 93]).

According to the study protocol, three additional trials were permitted, but only 10 infants (6 in the control group and 4 in the nitric oxide group) underwent such trials. Twenty-eight infants assigned to the control group (23 percent) received the study gas for more than 24 hours, as compared with 64 infants assigned to the nitric oxide group (56 percent) (median duration of gas administration, 2 hours vs. 40 hours; $P<0.001$). Among the infants who had responses to either the 20-ppm or the 80-ppm concentration of

TABLE 4. RESPONSES TO THE INITIAL ADMINISTRATION OF 20-ppm NITRIC OXIDE OR OXYGEN, AND SUBSEQUENT RESPONSES TO 80-ppm CONCENTRATIONS OF STUDY GAS BY INFANTS WHOSE RESPONSES TO THE INITIAL TREATMENT WERE LESS THAN COMPLETE.*

VARIABLE	CONTROL GROUP	NITRIC OXIDE GROUP	P VALUE†
	no. of patients (%)		
Response to treatment at 20 ppm			
No. of infants	117	112	
None	87 (74.4)	38 (33.9)	
Partial	13 (11.1)	17 (15.2)	<0.001
Complete	17 (14.5)	57 (50.9)	
Subsequent response to treatment at 80 ppm			
Infants with no response at 20 ppm			
None	64 (73.6)	29 (76.3)	
Partial	5 (5.7)	5 (13.2)	0.30
Complete	12 (13.8)	2 (5.3)	
80 ppm not tried	6 (6.9)	2 (5.3)	
Infants with partial responses at 20 ppm			
None	11 (84.6)	12 (70.6)	
Partial	1 (7.7)	4 (23.5)	0.34
Complete	0	1 (5.9)	
80 ppm not tried	1 (7.7)	0	

*Data on 229 infants are shown because 4 infants in the control group and 1 in the nitric oxide group did not receive study gas and data on 1 infant treated with nitric oxide were unavailable because of mechanical problems with gas delivery. Seven infants (six in the nitric oxide group and one in the control group) who received the wrong study gas are included in the table under their assigned treatments.

†P values are for the comparison between groups with respect to the number of infants with either a partial or a complete response to the study gas.

TABLE 5. RESULTS OF THE SUBGROUP ANALYSIS.

VARIABLE	NO. OF PATIENTS*	PERCENT WITH IMPROVED OXYGENATION†		PERCENT WITH PRIMARY OUTCOME‡		RELATIVE RISK (95% CI)§
		CONTROL	NITRIC OXIDE	CONTROL	NITRIC OXIDE	
Primary diagnosis						
Persistent pulmonary hypertension	41	14	61	73	32	0.43 (0.23–0.81)
Respiratory distress syndrome	25	8	60	47	50	1.07 (0.46–2.49)
Meconium aspiration	116	16	47	62	52	0.83 (0.61–1.15)
Pneumonia or sepsis	50	17	52	67	39	0.58 (0.33–1.00)
Pulmonary hypertension found by echocardiography						
Yes	176	15	54	65	47	0.72 (0.55–0.94)
No	50	14	44	50	39	0.79 (0.42–1.48)
Surfactant						
Yes	168	14	51	54	38	0.71 (0.51–0.99)
No	67	15	50	88	64	0.72 (0.55–0.95)
High-frequency ventilation						
Yes	130	14	57	66	46	0.70 (0.51–0.96)
No	105	16	43	61	45	0.74 (0.51–1.06)
Surfactant and high-frequency ventilation						
Both	88	13	59	57	37	0.64 (0.40–1.00)
Neither	25	14	40	93	64	0.69 (0.45–1.04)
Oxygenation index						
25.0–29.9	53	7	76	61	28	0.46 (0.24–0.88)
30.0–39.9	72	27	42	42	47	1.13 (0.67–1.91)
40.0–59.9	74	11	51	76	47	0.62 (0.43–0.89)
≥60.0	35	11	27	84	69	0.82 (0.56–1.18)

*Data on primary diagnosis are based on 232 patients; on pulmonary hypertension found by echocardiography, 226; and on oxygenation index, 234.

†Improved oxygenation was defined as a complete response (an increase of more than 20 mm Hg in the partial pressure of arterial oxygen) to the administration of 20-ppm nitric oxide or control gas at 30 minutes.

‡The primary study outcome was death by 120 days of age or the initiation of extracorporeal membrane oxygenation.

§Relative risks shown are for the occurrence of the primary study outcome in the nitric oxide group as compared with the control group. CI denotes confidence interval.

study gas when it was first administered, 62 percent of those in the nitric oxide group (50 of 81) were successfully weaned, as compared with 40 percent of those in the control group (19 of 47). Among the infants successfully weaned, three of those in the control group and two of those in the nitric oxide group had the study gas administered again.

Post hoc subgroup analyses were performed to evaluate the relations between each of several variables — the primary diagnosis, the presence or absence of echocardiographic evidence of pulmonary hypertension, the first qualifying oxygenation-index score, and treatment with surfactant before randomization, the use of high-frequency ventilation at the time of randomization or earlier, or the use of both surfactant and ventilation — and the incidence of the primary outcome and a complete response to the study gas (Table 5). Tests of homogeneity did not show significant differences between the relative risks. Therefore, there was no conclusive evidence, when the nitric oxide group was compared with the control group, that the relative risk either of the primary outcome or of a complete response to nitric oxide was related to any of the variables studied in the subgroup analysis.

Safety and Toxicity

The study gas was not discontinued in any infant because of toxic effects. In the nitric oxide group, the mean peak level of nitrogen dioxide was 0.8 ± 1.2 ppm, and the mean peak methemoglobin level was 2.4 ± 1.8 percent. The concentration of inhaled nitric oxide was reduced in 11 infants in the nitric oxide group because of elevated methemoglobin levels (5 to 10 percent).

There were no significant differences between the groups after randomization in the overall incidence or severity of intracranial hemorrhage (total number, 19 in the control group and 18 in the nitric oxide group; grade IV, 8 and 5, respectively). There were also no significant differences between the control group and the nitric oxide group in the occurrence of periventricular leukomalacia (6 vs. 3), brain infarction (7 vs. 7), seizures requiring anticonvulsive therapy (16 vs. 24), and either pulmonary (4 vs. 6) or gastrointestinal (1 vs. 1) hemorrhage.

There were 21 deviations from the protocol. Two infants who were ineligible for the study were randomized: one had a cystic adenomatoid malformation, and the other had a qualifying oxygenation-index score of 24.4. One infant randomly assigned to nitric oxide received oxygen, and six controls received nitric oxide. Two infants received doses of nitric oxide in excess of 80 ppm: 100 ppm for 36 minutes in one, and 101 ppm for 60 minutes in the other. The methemoglobin level in the latter was 6 percent, and the nitrogen dioxide concentration 5.1 ppm; these levels decreased when the dose of nitric oxide was lowered. Two infants received 80-ppm nitric oxide in error, after having complete responses to the 20-ppm concentration. There were eight episodes in which the patient's study assignment became apparent because of equipment leaks or elevated methemoglobin values.

DISCUSSION

This trial demonstrated that nitric oxide therapy reduced the incidence of death or extracorporeal membrane oxygenation in a cohort of full-term and nearly full-term infants with hypoxic respiratory failure who did not respond to aggressive conventional therapy. Furthermore, besides testing clinically important outcomes, the study was designed as a management trial whose findings could serve as the basis of recommendations for practice. Although inhaled nitric oxide reduced the combined outcome of death or the initiation of extracorporeal membrane oxygenation, it did not significantly reduce mortality, which was 17 percent in the control group and 14 percent in the nitric oxide group. The causes of death in the two groups did not differ. Among infants who received extracorporeal membrane oxygenation, overall mortality was 16 percent (14 percent in the control group and 18 percent in the nitric oxide group).

Several open-label studies preceding this trial reported improved oxygenation in infants with severe persistent pulmonary hypertension who were treated with initial doses of nitric oxide ranging from 5 to 80 ppm.[17-19] In the current trial, 47 percent of the infants treated with nitric oxide (53 of 112) received the 80-ppm concentration after having less than a complete response at 20 ppm. Only 15 percent of those infants (8 of 53) had improved responses (3 complete and 5 partial) at 80 ppm, suggesting that limited numbers of infants will benefit from higher doses of nitric oxide.

Nitric oxide treatment appears safe at the concentrations and durations used in this trial. However, the protocol was designed to reduce the likelihood of dose-related toxic effects by encouraging the use of the lowest effective dose. There was no evidence of toxic effects as determined on the basis of elevated levels of nitrogen dioxide, persistently elevated methemoglobin levels, systemic hypotension, or evidence of increased bleeding. The effect of inhaled nitric oxide on coagulation, platelet aggregation, and adhesion is unclear.[25-27] The study was not designed to evaluate the formation of peroxynitrites or evidence of other tissue damage that could potentially accompany the administration of nitric oxide.[28,29] Nor was it designed to determine the lowest effective dose of nitric oxide. Further research will be required to address these issues. All the infants in the current trial will receive a blinded neurodevelopmental evaluation at the age of 18 to 24 months.

We intended to treat infants who had an oxygenation index of 25 or above (50 percent risk of requiring extracorporeal membrane oxygenation or dying), but the majority had three oxygenation-index determinations exceeding 40 within a two-hour period, thereby meeting the most common criterion for extracorporeal membrane oxygenation before they were randomized.[30] Before extracorporeal membrane oxygenation was widely available, oxygenation indexes in this range predicted a risk of mortality of approximately 80 percent.[30] Although post hoc subgroup analyses did not show a significant difference in the relative risks, infants with the lowest oxygenation indexes appeared more likely to have complete responses to the initial administration of nitric oxide and to survive without extracorporeal membrane oxygenation, suggesting that the earlier use of nitric oxide may be beneficial. This question should be tested in a prospective trial. In the interim, nitric oxide therapy should not be delayed until the infant's condition is so unstable that transfer for extracorporeal membrane oxygenation would be difficult or impossible. We believe that appropriate support by conventional means, including the use of surfactant and high-frequency ventilation by experienced practitioners, should precede the administration of inhaled nitric oxide. If such management does not lead to improvement, however, treatment with nitric oxide, whether there is echocardiographic evidence of pulmonary hypertension or not, will substantially reduce the number of infants who receive extracorporeal membrane oxygenation.

Inhaled nitric oxide reduced the use of extracorporeal membrane oxygenation in critically ill neonates born at or near term with hypoxic respiratory failure who had received maximal conventional therapy. Nitric oxide therapy was safe, well tolerated, and relatively easy to administer.

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APPENDIX

The Neonatal Inhaled Nitric Oxide Study was a collaboration of the NICHD Neonatal Research Network and the Canadian Inhaled Nitric Oxide Study Group. The following institutions and investigators participated in the trial. (Members of the Executive Committee are indicated by asterisks.) **NICHD Neonatal Research Network:** *Case Western Reserve University, Cleveland* — E. Stork, E. Gorjanc; *George Washington University, Biostatistics Center, Rockville, Md.* — J. Verter,* N. Younes, B.A. Stenzel, T. Powers; *Indiana University, Indianapolis* — G. Sokol,* D. Appel; *NICHD, Bethesda, Md.* — L.L. Wright,* S.J. Yaffe, C. Catz; *Stanford University, Palo Alto, Calif.* — K. Van Meurs, W. Rhine,* B. Ball; *University of Cincinnati, Cincinnati* — R. Brilli, L. Moles; *University of New Mexico, Albuquerque* — M. Crowley, C. Backstrom; *University of Tennessee at Memphis* — D. Crouse, T. Hudson; *Wayne State University, Detroit* — G. Konduri,* R. Bara; *Women and Infants' Hospital, Providence, R.I.* — M. Kleinman, A. Hensman, R.W. Rothstein; *Yale University, New Haven, Conn.* — R.A. Ehrenkranz* (co-principal investigator). **Canadian Inhaled Nitric Oxide Study Group:** *British Columbia Children's Hospital, Vancouver* — A. Solimano,* F. Germain; *Children's Hospital of Eastern Ontario, Ottawa* — R. Walker, A.M. Ramirez; *Foothills Hospital, Calgary, Alta.* — N. Singhal, L. Bourcier; *Health Sciences Center, Winnipeg, Man.* — C. Fajardo, V. Cook; *McMaster University, Hamilton, Ont.* — H. Kirpalani,* S. Monkman; *Montreal Children's Hospital, Montreal* — A. Johnston,* K. Mullahoo; *Royal Alexandra Hospital, Edmonton, Alta.* — N.N. Finer* (co-principal investigator), A. Peliowski, P. Etches, B. Kamstra; *Royal University Hospital, Saskatoon, Sask.* — K. Sankarhan, A. Riehl; *Université de Sherbrooke, Sherbrooke, Que.* — P. Blanchard, R. Gouin; *Texas Children's Hospital, Houston* — M. Wearden, M. Gomez, Y. Moon. **NICHD Neonatal Research Steering Committee:** *University of Miami, Miami* — C.R. Bauer; *University of Cincinnati, Cincinnati* — E.F. Donovan; *Yale University, New Haven, Conn.* — R.A. Ehrenkranz; *Case Western Reserve University, Cleveland* — A.A. Fanaroff; *University of Tennessee at Memphis* — S.B. Korones; *Indiana University, Indianapolis* — J.A. Lemons; *Women and Infants' Hospital, Providence, R.I.* — W. Oh; *University of New Mexico, Albuquerque* — L.A. Papile; *Wayne State University, Detroit* — S. Shankaran; *Stanford University, Palo Alto, Calif.* — D.K. Stevenson; *Emory University, Atlanta* — B.J. Stoll; *University of Texas Southwestern Medical Center, Dallas* — J.E. Tyson; *George Washington University, Biostatistics Center, Rockville, Md.* — J. Verter; *NICHD, Bethesda, Md.* — L.L. Wright. **Data Safety and Monitoring Committee:** *Children's Hospital National Medical Center, Washington, D.C.* — G. Avery (chairman); *New England Medical Center, Boston* — M. D'Alton; *Yale University, New Haven, Conn.* — M.B. Bracken; *NICHD, Bethesda, Md.* — C. Catz (executive secretary); *Johns Hopkins Hospital, Baltimore* — C.A. Gleason; *University of Pennsylvania, Philadelphia* — M. Maguire; *University of Pittsburgh, Pittsburgh* — C. Redmond; *Greenbrae, Calif.* — W. Silverman; *McMaster University, Hamilton, Ont.* — J. Sinclair; *George Washington University, Biostatistics Center, Rockville, Md.* — J. Verter (ex officio).

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EXHIBIT 4

TO THE DECLARATION OF GEOFFREY L. ROSENTHAL, M.D. PH.D.

LOW-DOSE NITRIC OXIDE THERAPY FOR PERSISTENT PULMONARY HYPERTENSION OF THE NEWBORN

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ABSTRACT

Background Inhaled nitric oxide improves gas exchange in neonates, but the efficacy of low-dose inhaled nitric oxide in reducing the need for extracorporeal membrane oxygenation has not been established.

Methods We conducted a clinical trial to determine whether low-dose inhaled nitric oxide would reduce the use of extracorporeal membrane oxygenation in neonates with pulmonary hypertension who were born after 34 weeks' gestation, were 4 days old or younger, required assisted ventilation, and had hypoxemic respiratory failure as defined by an oxygenation index of 25 or higher. The neonates who received nitric oxide were treated with 20 ppm for a maximum of 24 hours, followed by 5 ppm for no more than 96 hours. The primary end point of the study was the use of extracorporeal membrane oxygenation.

Results Of 248 neonates enrolled, 126 were randomly assigned to the nitric oxide group and 122 to the control group. Extracorporeal membrane oxygenation was used in 78 neonates in the control group (64 percent) and in 48 neonates in the nitric oxide group (38 percent) ($P=0.001$). The 30-day mortality rate in the two groups was similar (8 percent in the control group and 7 percent in the nitric oxide group). Chronic lung disease developed less often in neonates treated with nitric oxide than in those in the control group (7 percent vs. 20 percent, $P=0.02$). The efficacy of nitric oxide was independent of the base-line oxygenation index and the primary pulmonary diagnosis.

Conclusions Inhaled nitric oxide reduces the extent to which extracorporeal membrane oxygenation is needed in neonates with hypoxemic respiratory failure and pulmonary hypertension. (N Engl J Med 2000;342:469-74.)

PERSISTENT pulmonary hypertension is common in neonates with respiratory failure.[1,2] It is characterized by pulmonary hypertension and extrapulmonary right-to-left shunting across the foramen ovale and ductus arteriosus. In many cases, the disease progressively worsens, becoming refractory to treatment.[3-5]

When other therapies fail, neonates are treated with extracorporeal membrane oxygenation.[3-5] This therapy improves survival in neonates with respiratory failure,[6-8] but its administration is labor-intensive and costly and necessitates large amounts of blood products. The mortality rate in neonates treated with extracorporeal membrane oxygenation is 15 to 20 percent, and 10 to 20 percent of the neonates who survive have substantial developmental delay.[7-12]

Nitric oxide is produced in vascular endothelial cells and plays an important part in increasing blood flow to the lungs after birth.[13-17] Exogenously administered nitric oxide causes selective pulmonary vasodilatation in newborn lambs,[13] and the administration of low doses of nitric oxide causes sustained improvement in gas exchange in neonates.[18] However, the efficacy of low-dose inhaled nitric oxide in reducing the use of extracorporeal membrane oxygenation has not been established. This study was undertaken to determine whether low-dose inhaled nitric oxide reduces the use of extracorporeal membrane oxygenation in neonates with pulmonary hypertension.

METHODS

Study Subjects

We studied 248 neonates who were born after 34 weeks' gestation, were 4 days old or younger, required assisted ventilation, and had an oxygenation index of 25 or higher. The oxygenation index was calculated as the mean airway pressure times the fraction of inspired oxygen times 100, divided by the partial pressure of arterial oxygen. The neonates had clinical or echocardiographic evidence of pulmonary hypertension without structural heart disease. Clinical evidence of pulmonary hypertension was defined as a difference of 5 percent between preductal and postductal oxygen saturation or recurrent (more than two) decreases in arterial oxygen saturation (to less than 85 percent) in a period of 12 hours despite optimal treatment of lung disease. Echocardiographic evidence of pulmonary hypertension was defined as an estimated peak systolic pulmonary-artery pressure that was higher than 35 mm Hg or more than two thirds of the systemic systolic pressure as indicated by a tricuspid regurgitant jet, a right-to-left ductus arteriosus shunt, or a right-to-left atrial-level shunt. In addition, we considered as study candidates neonates in whom extreme alkalosis (a pH higher than 7.55) was required to maintain a partial pressure of arterial oxygen of more than 60 mm Hg.

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Pre-enrollment treatment with high-frequency ventilation (model 3100A, SensorMedics, Yorba Linda, Calif.) or surfactant was encouraged. Neonates were not eligible for the study if extracorporeal membrane oxygenation was urgently needed for refractory hypotension (a mean blood pressure lower than 35 mm Hg) or profound hypoxemia (a partial pressure of arterial oxygen lower than 30 mm Hg) or if they had a lethal congenital anomaly, a substantial bleeding diathesis, active seizures, or a history of severe asphyxia. The study was approved by the institutional review board at each study site, and written informed consent was obtained from a parent or guardian.

Randomization

To balance the distribution of pulmonary-disease diagnoses in the two treatment groups, each neonate was assigned to one of five diagnostic categories and then randomly assigned to treatment. The diagnostic categories were the meconium aspiration syndrome, which was diagnosed on the basis of a history of meconium-stained amniotic fluid and abnormal results on chest radiography; pneumonia, with two or more risk factors for sepsis and no history that suggested lung immaturity (the risk factors for sepsis were maternal chorioamnionitis, maternal fever, positive vaginal culture for group B streptococcus, a white-cell count of more than 30,000 cells per cubic millimeter or less than 5000 cells per cubic millimeter, a ratio of immature to total neutrophils of more than 0.2, a serum C-reactive protein concentration of more than 2 μg per milliliter, hypotension that required vasopressor support, and coagulopathy); the respiratory distress syndrome, with fewer than two risk factors for sepsis, a history that suggested lung immaturity, and a chest radiograph that had a reticulogranular appearance; lung hypoplasia syndromes, which were diagnosed on the basis of the presence of a congenital diaphragmatic hernia, a history of prolonged oligohydramnios, or hydrops fetalis; and idiopathic persistent pulmonary hypertension, which required a clinical diagnosis of pulmonary hypertension and a chest radiograph showing little or no lung disease.

Cards on which treatment assignments were written were randomly ordered (shuffled by hand three times) at Emory University in Atlanta and placed in sequentially numbered opaque envelopes in blocks of eight for diagnostic-category strata 1, 2, and 3 and in blocks of four for strata 4 and 5; the number in each block reflected the anticipated frequencies of diagnoses. Notebooks in which the numbered envelopes were stored were sent to each study site.

After the attending physician obtained consent, a respiratory therapist was told the neonate's diagnostic stratum and identified the appropriate sequentially ordered envelope. The therapist then set up the system of treatment delivery, completed the basic information on the randomization card, and mailed the card to the center that coordinated the study. The study coordinator at the coordinating center monitored the order in which the treatment cards were used.

Neither the physicians nor the nurses were told the treatment assignments. Respiratory therapists directed treatment and made adjustments to keep the concentration of nitric oxide within the prescribed range ($\pm$10 percent of the target dose). In the first 36 neonates enrolled, the delivery systems for the two treatment groups were identical. The neonates assigned to the control group were treated by continuing the flow of oxygen without initiating the administration of nitric oxide. In the remaining 212 neonates, nitrogen (delivered through the INO Delivery System, Ohmeda, Madison, Wis.) was used as the control to improve the masking of the treatment assignment. The gas tank and monitor readouts were covered so that the tank and the monitored values for nitric oxide and nitrogen dioxide could not be seen.

Treatment Guidelines and Delivery of Gas

In the first 18 neonates in the treatment group, nitric oxide gas (Scott Medical Products, Plumstead, Pa.) was delivered from a 450-ppm cylinder. Nitric oxide was introduced into the afferent limb of the ventilator circuit near the endotracheal tube, thus mixing with the fixed flow of gas in the ventilator circuit. The flow was adjusted to yield the assigned concentrations of nitric oxide. Nitric oxide and nitrogen dioxide were measured with electrochemical monitors (Pac II nitric oxide monitor and model 190 nitrogen dioxide monitor, Drager, Chantilly, Va.). For the 108 remaining neonates in the nitric oxide group, nitric oxide gas (INO Therapeutics, Port Allen, La.) was delivered from an 800-ppm cylinder. The control subjects received 100 percent nitrogen (Ohmeda, BOC Gases, Murray Hill, N.J.). The study gas (nitrogen or nitric oxide) was delivered (with the INO Delivery System) into the inspiratory flow of the ventilator circuit. The device measured the flow of gas in the ventilator circuit, and a mass-flow controller added study gas to the ventilator circuit to create the desired concentration. The device continuously sampled gas from the endotracheal side-port adapter and measured oxygen, nitric oxide, and nitrogen dioxide with electrochemical monitors. Inhaled nitric oxide and nitrogen had a similar effect on the fraction of inspired oxygen (reducing the value to 0.98).[19]

The administration of the study gas (nitrogen or nitric oxide) was started at 20 ppm, and this amount was continued for four hours. At four hours, arterial-blood gases and methemoglobin were measured. The dose was decreased to 5 ppm if the neonate's condition was stable, the partial pressure of arterial oxygen was at least 60 mm Hg, and the pH was 7.55 or lower. If these criteria were not met, the administration of study gas was maintained at 20 ppm, and the neonate was evaluated every 4 hours until the criteria were met or the neonate had been treated for 24 hours. During the first 24 hours, the dose of study gas could be returned to 20 ppm if the neonate's partial pressure of arterial oxygen fell below 60 mm Hg when the fraction of inspired oxygen was 1.0. After 24 hours of treatment, the dose was decreased to 5 ppm. Treatment was continued at 5 ppm until the fraction of inspired oxygen was less than 0.7, the neonate had been treated for 96 hours, or the neonate was seven days old, whichever came first.

If the neonate did not tolerate the decreased dose at 24 hours or if at 96 hours the study gas could not be discontinued, the treatment was considered a failure. If a clinical decision was made to proceed with extracorporeal membrane oxygenation, the study gas was continued until it was started.

Methemoglobin was measured at base line and at 4, 24, and 96 hours while the neonate was receiving the study gas. The concentration of study gas was reduced by half if the neonate had a methemoglobin value of more than 4 percent or a nitrogen dioxide concentration of more than 5 ppm, and the administration of the study gas was discontinued if these values did not become normal.

We aimed to achieve the following blood gas values in the neonates: a partial pressure of arterial oxygen of 60 to 100 mm Hg; a partial pressure of arterial carbon dioxide of 25 to 30 mm Hg and a pH of 7.40 to 7.55 in neonates with a response to alkalosis; and a partial pressure of arterial carbon dioxide of 35 to 45 mm Hg and a pH of 7.35 to 7.45 in neonates with no response to alkalosis. The target mean blood pressure was 45 to 60 mm Hg.

Criteria for Discontinuing Treatment in the Study

Treatment was discontinued if the neonate was successfully weaned from the study gas, met the criteria for treatment failure, or met the criteria for extracorporeal membrane oxygenation. Neonates who met the criteria for treatment failure were not automatically treated with extracorporeal membrane oxygenation. The criteria for the use of extracorporeal membrane oxygenation were an oxygenation index of more than 40 on three of five measurements performed at least 30 minutes apart; a partial pressure of arterial oxygen lower than 40 mm Hg for 2 hours; or progressive hemodynamic deterioration (a mean blood pressure below 35 mm Hg). The decision to use extracorporeal membrane oxygenation was made by the attending physician and by the consulting team for extracorporeal membrane oxygenation.

Study End Points

Our primary hypothesis was that the use of extracorporeal membrane oxygenation would be the same in neonates treated with

nitric oxide and those not treated with nitric oxide. Our secondary hypotheses were that the two groups would have the same improvement in the ratio of arterial oxygen to alveolar oxygen, the same incidence of short-term complications (hypotension, methemoglobinemia, and deterioration in gas exchange), the same incidence of long-term complications (chronic lung disease and neurologic handicaps), and the same incidence of death. The results presented here are for follow-up at 30 days; the results of follow-up at 1 year are being collected now.

Statistical Analysis

We evaluated categorical variables using two-tailed chi-square and Fisher's exact tests. Continuous variables were compared with use of a two-tailed t-test or the Kruskal–Wallis test. Ranked data were assessed with the two-tailed Kruskal–Wallis test. We compared changes over time in the two groups of neonates with regard to gas exchange, methemoglobin values, and nitrogen dioxide concentrations, using analysis of variance for repeated measures. We used a multivariate logistic-regression analysis to evaluate the independent effects of the following covariates on the use of extracorporeal membrane oxygenation and the occurrence of chronic lung disease: treatment group, sex, surfactant treatment, support with high-frequency ventilation, air leak (pneumothorax, pulmonary interstitial emphysema, or pneumomediastinum) at study entry, age at study entry, primary pulmonary diagnosis, and oxygenation index.

RESULTS

Base-Line Characteristics

Two hundred forty-eight neonates were enrolled in the study; 126 were assigned to the nitric oxide group, and 122 to the control group. The base-line characteristics of the two treatment groups were similar, with the exception of prenatal care before the third trimester and the presence of an air leak before enrollment (Table 1). However, there were no differences in obstetrical complications, and all air leaks were stabilized before enrollment.

As compared with the nitric oxide group, the control group had a higher mean (±SD) blood pressure (55±12 mm Hg vs. 51±11 mm Hg, P=0.02) and a lower partial pressure of arterial oxygen (58±42 mm Hg vs. 72±64 mm Hg, P=0.05) (Table 2). However, the mean level of pressor support and the severity of hypoxemia, assessed by the oxygenation index, were similar in the two groups (Tables 1 and 2). There were no differences between the two groups in the incidence of echocardiographic evidence of pulmonary hypertension.

TABLE 1. BASE-LINE CHARACTERISTICS OF THE STUDY SUBJECTS.*

CHARACTERISTIC	CONTROL GROUP (N=122)	NITRIC OXIDE GROUP (N=126)	P VALUE
Prenatal care before third trimester — no. (%)	101 (83)	116 (92)	0.02
Birth weight — kg	3.3±0.6	3.3±0.5	0.59
Male sex — no. (%)	73 (60)	60 (48)	0.06
Referred from another hospital — no. (%)	83 (68)	92 (73)	0.38
Race or ethnic group — no. (%)			0.38
Non-Hispanic black	41 (34)	49 (39)	
Hispanic	14 (11)	10 (8)	
Non-Hispanic white	67 (55)	67 (53)	
Primary pulmonary diagnosis — no. (%)			0.80
Meconium aspiration syndrome	42 (34)	43 (34)	
Pneumonia	26 (21)	26 (21)	
Idiopathic pulmonary hypertension	25 (20)	32 (25)	
Respiratory distress syndrome	11 (9)	11 (9)	
Congenital diaphragmatic hernia	18 (15)	13 (10)	
Pulmonary hypoplasia	0	1 (1)	
Lung disease — no. (%)†			0.50
None	10 (8)	16 (13)	
Mild	31 (25)	33 (26)	
Moderate	57 (47)	51 (40)	
Severe	24 (20)	26 (21)	
Air leak before enrollment — no. (%)	29 (24)	16 (13)	0.03
Drugs used before enrollment — no. (%)			
Surfactant	52 (43)	43 (34)	0.19
Sodium bicarbonate	89 (73)	97 (77)	0.47
Vasopressors (dopamine, dobutamine, and epinephrine)	109 (89)	110 (87)	0.86
Age at enrollment — hr	28±17	28±20	0.77

*Plus–minus values are means ±SD.

†The severity of lung disease was determined on the basis of chest radiography. None indicates no radiographic signs of lung disease; mild indicates minimal streaky infiltrates or reticulogranular changes with easily visualized borders of the heart and diaphragm; moderate indicates diffuse infiltrates or reticulogranular changes with obscure but visible borders of the heart and diaphragm; and severe indicates diffuse infiltrates with borders of the heart and diaphragm that were difficult to visualize.

Deviations from the Protocol

Two neonates assigned to the control group were treated with nitric oxide; both were included in the control group in an intention-to-treat analysis. There were 21 deviations from the protocol. In 12 neonates, an oxygenation index higher than 25 at base line was not documented adequately. Three neonates had partial pressures of arterial oxygen that were lower than 30 mm Hg at base line and thus fulfilled the criteria for exclusion because of their urgent need for extracorporeal membrane oxygenation. Two neonates did not have pulmonary hypertension. Four other neonates should not have been enrolled in the study, because they had congenital heart disease, seizures, an estimated gestational age of less than 34 weeks, or a lethal anomaly (an inoperable cystic hygroma).

Primary Outcome

The use of extracorporeal membrane oxygenation was less common in the nitric oxide group than in the control group (38 percent vs. 64 percent, P=0.001) (Table 3). This was true in all pulmonary diagnostic groups except neonates with congenital diaphragmatic hernia (Table 4). In the neonates treated with extracorporeal membrane oxygenation, the median time from the start of treatment to the start of extracorporeal membrane oxygenation was similar in the two groups (5 hours in the control group [range, 1 to 86] and 9 hours in the nitric oxide group [range, 2 to 150]). Eight neonates (three in the control group and

TABLE 2. BASE-LINE VENTILATORY STATUS OF THE STUDY SUBJECTS.*

VARIABLE	CONTROL GROUP (N=122)	NITRIC OXIDE GROUP (N=126)	P VALUE
Receiving high-frequency oscillation — no. (%)	72 (59)	62 (49)	0.10
Receiving conventional mechanical ventilation — no. (%)	46 (38)	59 (47)	0.10
FiO_2			
Neonates assessed — no. (%)	118 (97)	125 (99)	
Mean value	1.0±0.03	1.0±0.03	0.64
Peak pressure†			
Neonates assessed — no. (%)	46 (38)	59 (47)	
Mean value — cm of water	33±7	33±7	0.64
Pressure amplitude‡			
Neonates assessed — no. (%)	69 (57)	62 (49)	
Mean value — cm of water	42±11	42±11	0.94
Rate for high-frequency oscillation			
Neonates assessed — no. (%)	70 (57)	62 (49)	
Mean value — Hz	10±1	10±2	0.27
Rate for conventional mechanical ventilation			
Neonates assessed — no. (%)	46 (38)	59 (47)	
Mean value — breaths/min	57±13	58±14	0.63
Mean airway pressure			
High-frequency oscillation			
Neonates assessed — no. (%)	69 (57)	62 (49)	
Mean value — cm of water	20±4	20±4	0.72
Conventional mechanical ventilation			
Neonates assessed — no. (%)	43 (35)	55 (44)	
Mean value — cm of water	16±3	15±4	0.21
Arterial-blood gas values			
pH			
Neonates assessed — no. (%)	114 (93)	119 (94)	
Mean value	7.44±0.1	7.45±0.1	0.35
PaO_2			
Neonates assessed — no. (%)	113 (93)	119 (94)	
Mean value — mm Hg	58±42	72±64	0.05
$PaCO_2$			
Neonates assessed — no. (%)	113 (93)	119 (94)	
Mean value — mm Hg	36±12	35±13	0.68
Oxygenation index§			
Neonates assessed — no. (%)	107 (88)	111 (88)	
Mean value	41±21	37±24	0.17

*Values are not included for neonates who were receiving manual ventilation at base line or for whom blood gas values were obtained after the start of treatment. FiO_2 denotes fraction of inspired oxygen, PaO_2 partial pressure of arterial oxygen, and $PaCO_2$ partial pressure of arterial carbon dioxide. Plus–minus values are means ±SD.

†These values are for neonates who were receiving conventional ventilation.

‡These values are for neonates who were receiving high-frequency oscillation.

§The oxygenation index was calculated as the mean airway pressure times the fraction of inspired oxygen times 100, divided by the partial pressure of arterial oxygen.

five in the nitric oxide group) met the criteria for extracorporeal membrane oxygenation but did not receive it. All survived to discharge, and chronic lung disease did not develop in any of them. Four neonates who were not treated with extracorporeal membrane oxygenation died. Two died after prolonged assisted ventilation; one of these neonates had adenoviral bronchiolitis obliterans, and the other had severe chronic lung disease. The other two neonates who died had contraindications to treatment with extracorporeal membrane oxygenation: one had uncontrolled bleeding, and the other had an inoperable cystic hygroma.

Secondary Outcomes

Twenty-three neonates died before discharge: 13 in the control group and 10 in the nitric oxide group ($P=0.82$). There were no differences between the two groups in terms of the cause of death.

After one hour of treatment, the ratio of arterial to alveolar oxygen increased more in the nitric oxide group than in the control group (by 0.10 ± 0.14 vs. 0.05 ± 0.13, $P=0.02$). There was no difference between the two groups with regard to ventilator settings, heart rate, mean blood pressure, or level of dopamine support during the first four hours of treatment.

Thirty neonates had chronic lung disease (as determined by the need for supplemental oxygen at 30 days). Nineteen neonates died before 30 days of age. In the group of 224 survivors for whom data were available, the incidence of chronic lung disease was lower in the neonates treated with nitric oxide than in the neonates in the control group (7 percent vs. 20 percent, $P=0.02$).

Among the survivors, there was no difference between the two treatment groups with regard to age at discharge, age at extubation, or duration of extracorporeal membrane oxygenation. Neurologic abnormalities occurred at the same rate in the two groups (Table 3).

The use of nitric oxide independently affected both the use of extracorporeal membrane oxygenation and the occurrence of chronic lung disease. A high oxygenation index, assignment to the control group, and a diagnosis of congenital diaphragmatic hernia were all associated with the use of extracorporeal membrane oxygenation. The most important factor that affected the development of chronic lung disease was the diagnosis of congenital diaphragmatic hernia. The oxygenation index and the presence of an air leak before enrollment in the study were not independent predictors of chronic lung disease.

DISCUSSION

We found that the administration of low doses of nitric oxide reduced the use of extracorporeal membrane oxygenation and decreased the need for supplemental oxygen at 30 days in neonates with hypoxemic respiratory failure and persistent pulmonary hypertension. We stratified the neonates in both groups according to the diagnosis in order to assess the relative efficacy of treatment across diagnostic groups and to minimize the effect of underlying disease as a confounding variable. Our results confirm the findings of the Neonatal Inhaled Nitric Oxide

TABLE 3. OUTCOME ANALYSIS.*

OUTCOME	CONTROL GROUP (N=122)	NITRIC OXIDE GROUP (N=126)	P VALUE
Received extracorporeal membrane oxygenation			
Intention-to-treat analysis — no./total no. (%)	78/122 (64)	48/126 (38)	0.001
Neonates with no protocol violations — no./total no. (%)	74/116 (64)	43/111 (39)	0.001
Died before 30 days of age — no. (%)	10 (8)	9 (7)	0.40
Died before discharge — no. (%)	13 (11)	10 (8)	0.82
Died before discharge or received extracorporeal membrane oxygenation — no. (%)	80 (66)	50 (40)	0.001
Length of stay in the hospital for survivors			
Neonates assessed — no. (%)	104 (85)	113 (90)	0.09
Mean no. of days	29±23	25±15	
Duration of assisted ventilation for survivors			
Neonates assessed — no. (%)	109 (89)	116 (92)	0.40
Mean no. of days	12±10	11±7	
Pulmonary outcome in survivors			
Were receiving supplemental oxygen at 30 days — no./total no. (%)†	22/110 (20)	8/114 (7)	0.02
Received supplemental oxygen after discharge — no./total no. (%)†	12/107 (11)	6/113 (5)	0.14
Intraventricular hemorrhages (more than two) or infarct — no. (%)	8 (7)	4 (3)	0.34
Seizures — no. (%)	1 (1)	1 (1)	0.49

*Plus–minus values are means ±SD.

†Data were missing for five neonates (two in the control group and three in the nitric oxide group); these neonates were transported back to the referring hospitals, so data were not available at 30 days.

TABLE 4. RELATIVE RISK OF EXTRACORPOREAL MEMBRANE OXYGENATION ACCORDING TO DIAGNOSIS.

DIAGNOSIS	EXTRACORPOREAL MEMBRANE OXYGENATION		RELATIVE RISK (95% CI)*
	CONTROL GROUP (N=122)	NITRIC OXIDE GROUP (N=126)	
	no./total no. (%)		
Meconium aspiration syndrome	26/42 (62)	15/43 (35)	0.6 (0.3–0.9)
Pneumonia	18/26 (69)	9/26 (35)	0.5 (0.3–0.9)
Idiopathic pulmonary hypertension	9/25 (36)	9/32 (28)	0.8 (0.3–1.9)
Respiratory distress syndrome	9/11 (82)	3/11 (27)	0.3 (0.1–0.9)
Congenital diaphragmatic hernia	16/18 (89)	12/13 (92)	1.0 (0.8–1.2)
Pulmonary hypoplasia	0	0/1	

*The relative risk is expressed as the risk of a need for extracorporeal membrane oxygenation in the group of neonates treated with nitric oxide as compared with the control group. CI denotes confidence interval.

Study that nitric oxide is effective across a broad range of diagnoses.[20] The only exception was neonates with congenital diaphragmatic hernia, in whom nitric oxide did not reduce the use of extracorporeal membrane oxygenation or improve the outcome.[21]

The most important difference between our trial and previous studies is that we used a low dose of inhaled nitric oxide for a limited amount of time (a maximum of 96 hours). Other trials have used higher doses (80 ppm) for longer periods (as long as two weeks).[19,20,22] By limiting the duration of treatment, we hoped to avoid delaying extracorporeal membrane oxygenation beyond the point at which its efficacy might be reduced. Our data, combined with the results of previous studies, suggest that this approach is effective. In the Neonatal Inhaled Nitric Oxide Study, neonates who did not have a response to 20 ppm of nitric oxide rarely had a response to 80 ppm.[20] The median duration of successful treatment in our study was 44 hours, and all but two neonates were weaned from nitric oxide by 96 hours.

The potentially toxic effects of inhaled nitric oxide at high doses include decreased platelet aggregation,[15] an increased risk of bleeding,[23-25] acute lung injury as a result of oxidant injury,[26-29] and surfactant dysfunction.[30] In our study, none of the neonates had high concentrations of nitrogen dioxide, only two had high methemoglobin values, and nitric oxide was not associated with an increase in the occurrence of intracranial hemorrhages or chronic lung disease. In fact, nitric oxide was associated with a decrease in the occurrence of chronic lung disease.

The strength of the association between treatment with nitric oxide and an improved pulmonary outcome is demonstrated by the fact that the association remained significant in multivariate and subgroup analyses. The reason for this improvement is unclear. One possibility is that inhaled nitric oxide reduces lung inflammation. Studies in animals suggest that inhaled nitric oxide may reduce the accumulation of neutrophils in the lung and the attendant inflammatory cascade that contributes to acute lung injury.[31-33] Another possibility is that nitric oxide reduces ventilator-induced lung injury by improving gas exchange and reducing the intensity of required ventilatory support.

In conclusion, low-dose inhaled nitric oxide reduces the need for extracorporeal membrane oxygenation and reduces the occurrence of chronic lung disease in neonates with hypoxemic respiratory failure that does not result from congenital diaphragmatic hernia.

Supported in part by a grant from INO Therapeutics.

Dr. Clark has acted as a consultant to INO Therapeutics regarding the submission of data to the Food and Drug Administration. He is also the principal investigator for the grant that supported this study. Dr. Kinsella has acted as a consultant to INO Therapeutics regarding the submission of data to the Food and Drug Administration. Mrs. Huckaby has acted as a clinical research associate for INO Therapeutics in monitoring this study.

We are indebted to all the parents who agreed to allow their children to participate in this study; to Ms. Barbara Reynolds for her tireless administrative assistance; to Mr. Alex Stenzler for his help with the development of the protocol; to Dr. Richard Straube for his careful review of the manuscript and for statistical evaluation of our data; to Mr. Jared Rhines for coordinating data monitoring, meetings of investigators, and the delivery of drugs to the study sites; and to Dr. George Brumley, Dr. Devn Cornish, and Dr. Steve Abman for their support during the course of the study.

APPENDIX

In addition to the authors, the following institutions and investigators participated in the Clinical Inhaled Nitric Oxide Research Group: *Akron, Ohio* — J. Butler, K. Wellendorf; *Durham, N.C.* — K. Auten; *Phoenix, Ariz.* — D. Hall, E. Ramthun; *Atlanta* — L. Jain, I. Seabrook; *Washington, D.C.* — P. Angelus; *Charlotte, N.C.* — L. Brucoli; *Columbia, S.C.* — D. Marsh, A. O'Dell; *New Orleans* — M. McGettigan, B. Quinn, G. Matranga; *St. Petersburg, Fla.* — A. Napolitano, R. Williams; *San Antonio, Tex.* — M. Odom; *Orlando, Fla.* — J. Ramos; *Chicago* — M. Rathi, A. Shukla, T. Gardner; *Charleston, S.C.* — D. Purohit, S. Ballard, M. Nussbaum; *Sioux Falls, S D.* — D. Stevens, R. Klinghagen; *Greenville, S.C.* — V. Jenkinson; *Nashville* — W. Walsh, S. Steele, B. Canter; *Lackland AFB, Tex.* — B. Yoder, S. Woodcox.

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EXHIBIT 5

TO THE DECLARATION OF GEOFFREY L. ROSENTHAL, M.D. PH.D.

Exhibit E

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE (USPTO)	
Application Serial Number	12/820,866
Confirmation Number	2913
Filing Date	June 22, 2010
Title of Application	Methods of Treating Term and Near-Term Neonates Having Hypoxic Respiratory Failure Associated with Clinical or Echocardiographic Evidence of Pulmonary Hypertension
First Named Inventor	James S. Baldassarre
Assignee	Ikaria, Inc.
Group Art Unit	1613
Examiner	Arnold, Ernst V.
Attorney Docket Number	I001-0002USC1

Mail Stop Amendment
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, declare the following:

1. I currently hold the position of Vice President of Clinical Research at Ikaria, Inc. ("Ikaria"), the assignee of U.S. Patent Application No. 12/820,866. My *curriculum vitae* is attached as Exhibit 1.

2. I have over 20 years of experience as a physician, and over fifteen years of experience directing clinical research in the pharmaceutical industry.

3. 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, for the treatment of term and near-term (>34 weeks) neonates with hypoxic respiratory failure (HRF) associated with clinical or echocardiographic evidence of pulmonary hypertension, where it improves oxygenation and reduces the need for extracorporeal membrane oxygenation (ECMO).

4. In May 2004, INO Therapeutics LLC[1] 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", and designated the INOT22 trial, to compare the utility and side effects of oxygen (O_2), nitric oxide (iNO) and a combination of iNO and O_2 for determining pulmonary reactivity.

5. The INOT22 study was to be an open, prospective, randomized, multi-center, controlled diagnostic trial, with an expected total enrollment of a minimum of 150 patients, in approximately 18 study sites over approximately 2 years.

6. The expected patient population for enrollment into the INOT22 trial were subjects between the ages of four (4) weeks and eighteen (18) years undergoing diagnostic right heart catheterization scheduled to include acute pulmonary vasodilation testing to assess pulmonary vasoreactivity. The expected population were subjects with idiopathic pulmonary arterial hypertension, congenital heart disease (with or without intravascular shunt) with pulmonary hypertension and cardiomyopathies.

7. The INOT22 study was established and designed by the study sponsor, INO Therapeutics LLC (INO), and a Steering Committee comprising internationally recognized experts in the field of pediatric heart and lung disease, whose members would assist INO to develop the INOT22 protocol, monitor the progress of the trial, and provide recommendations to INO on changes in the procedures and conduct of the trial.

8. The Steering Committee consisted of:

a. David L. Wessel, MD, presently Division Chief, Pediatric Critical Care Medicine at Children's National Medical Center, Washington, DC (co-author of Atz., et al., Seminars in Perinatology);[2]

[1] INO Therapeutics LLC is a wholly owned subsidiary of Ikaria, Inc., and holder of the NDA for INOMAX.
[2] Cited in pending Office Action.

b. Robyn J. Barst, MD, presently 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, U.K. (lead author of Macrae, et al., Intensive Care Medicine, 2004)[3]

9. The original INOT22 protocol designed by INO 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 >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.

[3] Cited in pending Office Action.

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 +).

10. The INOT22 investigational plan and study protocol was further reviewed, and approved by the Institutional Review Board (IRB) and/or Independent Ethics Committee (IEC) at each of the participating study institutions, including review by the principal investigator within each study institution.

11. At no time did any member of the Steering Committee, nor any member of an IRB, IEC, or individual principal investigator, appreciate, recognize or otherwise suggest that the exclusion criteria be amended to exclude study subjects with pre-existing left ventricular dysfunction (LVD), due to an anticipated or predicted risk of adverse events or serious adverse events arising from the use of iNO in patients with pre-existing LVD, and/or elevated pulmonary capillary wedge pressure. Nor was it, in my expert opinion, common sense to any expert in this field of medicine to exclude neonates, near-term neonates or children diagnosed with pre-existing LVD to be excluded from having iNO administered for diagnostic or treatment purposes.

12. 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 iNO 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).

13. Thereafter, in February 2005, INO 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 iNO in subjects having pre-existing LVD . Accordingly, based upon a review of the cases, the exclusion criteria of the INOT22 protocol was amended to thereafter exclude subjects with pre-existing LVD. For the purpose of the study, the exclusion criteria was 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 (see point 5.) was 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*

14. Upon conclusion of the INOT22 study and completion of the final study report, INO noted that subsequent to excluding patients with pre-existing LVD, the rate of serious adverse events (including serious adverse events associated with heart failure) was significantly reduced. There were 5 SAEs amongst the first 24 subjects

prior to the additional exclusion criteria, but only 2 SAEs amongst the last 80 subjects in the study after the additional exclusion. Furthermore, there were 2 SAEs amongst 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.

15. Based upon this unexpected finding, on February, 25, 2009, INO submitted a labeling supplement to the FDA seeking to amend the prescribing information for INOMAX to include a warning statement for physicians such that the use of iNO in patients with pre-existing LVD could cause serious adverse events, such as pulmonary edema.

16. On August 28, 2009, the FDA approved the INO labeling supplement and included (i) a statement in the Warnings and Precautions section of the INOMAX prescribing information that states "Heart Failure: In patients with pre-existing left ventricular dysfunction, inhaled nitric oxide may increase pulmonary capillary wedge pressure leading to pulmonary edema", and (ii) new section 5.4 of the INOMAX prescribing information that states "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)."

17. Based upon my review of the medical literature of record in this patent application and pending Office Action, none of the prior art suggests, appreciates or otherwise recognizes that exclusion of neonates, near-term neonates or children with LV dysfunction from administration of iNO for diagnostic or treatment purposes would reduce the risk of adverse events and/or serious adverse events, as such terminology is well understood in the medical arts.

18. 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 from this patent application.

Dated: Sept 29, 2010

James S. Baldassarre, M.D.

EXHIBIT 6

TO THE DECLARATION OF GEOFFREY L. ROSENTHAL, M.D. PH.D.

Exhibit F

UNITED STATES PATENT AND TRADEMARK OFFICE	
Application Serial Number	12/820,866
Confirmation Number	2913
Filing Date	22-JUN-2010
Title of Application	METHODS OF TREATING TERM AND NEAR-TERM NEONATES HAVING HYPOXIC RESPIRATORY FAILURE ASSOCIATED WITH CLINICAL OR ECHOCARDIOGRAPHIC EVIDENCE OF PULMONARY HYPERTENSION
First Named Inventor	JAMES S. BALDASSARRE
Assignee	IKARIA, INC.
Group Art Unit	1616
Examiner	ARNOLD, ERNST V.
Attorney Docket Number	I001-0002USC1

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

DECLARATION OF JAMES S. BALDASSARRRE, M.D.
UNDER 37 C.F.R. § 1.132

I, James S. Baldassarre, do hereby declare the following:

1. I currently hold the position of Vice President of Clinical Research at INO Therapeutics LLC ("INO"), which is a wholly-owned subsidiary of Ikaria, Inc. A copy of my *curriculum vitae* is attached as **Exhibit 1.**

2. I have over 20 years of experience as a physician and over fifteen years of experience directing clinical research in the pharmaceutical industry.

3. In 2004, I was the Medical Monitor responsible for the design and execution of the INOT22 study.

4. 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 a randomized, multi-center study having an expected

enrollment of 150 patients, aged four weeks to 18 years, in approximately 18 study sites over approximately 2 years.

5. The INOT22 study was established and designed by the study sponsor, INO Therapeutics LLC and a Steering Committee comprising international recognized experts in the field of pediatric heart and lung disease, whose members would assist INO to develop the INOT22 protocol, monitor the progress of the trial, and provide recommendations to INO on changes in the procedures and conduct of the trial

6. 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, presently 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.

7. The original INOT22 study protocol designed by INO 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.

8. 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). In addition, INO regularly requested input and scientific guidance on clinical trials from its own Scientific Advisory Board At no time did any member of the Steering Committee, INOT, an IRB, IEC, individual principal investigator, Advisory Board member, FDA or European Health Authority appreciate, recognize or otherwise 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 anticipated or predicted to have an increased risk of adverse events or serious adverse events arising from the administration to them of inhaled nitric oxide.

9. 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 if sufficient and the appropriate safeguards have been put in place (see 21 CFR Part 56).

10. In Europe, an Ethics Committee is an independent body in a 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 adequacy of facilities involved in a trial (see Directive 2001/20/EC).

11. 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 initiating the INOT22 study. Again, not a single individual or authority suggested, predicted or 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 are not dependent on right-to-left shunt.

12. On the contrary, it was only after unexpected serious adverse events (including at least one death) occurred during the course of the INOT22 study that the study protocol was amended to exclude study subjects with pre-existing left ventricular dysfunction who are not dependent on right-to-left shunt. In particular, the exclusion criteria of the INOT22 study was amended to exclude subjects having an elevated pulmonary capillary wedge pressure greater than 20 mm Hg.

13. 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 the '359 patent.

Dated: 7 July 2011

James S. Baldassarre, M.D.

EXHIBIT 7

TO THE DECLARATION OF GEOFFREY L. ROSENTHAL, M.D. PH.D.

Exhibit C

UNITED STATES PATENT AND TRADEMARK OFFICE	
Application Serial Number	12/820,866
Confirmation Number	2913
Filing Date	22-JUN-2010
Title of Application	METHODS OF TREATING TERM AND NEAR-TERM NEONATES HAVING HYPOXIC RESPIRATORY FAILURE ASSOCIATED WITH CLINICAL OR ECHOCARDIOGRAPHIC EVIDENCE OF PULMONARY HYPERTENSION
First Named Inventor	JAMES S. BALDASSARRE
Assignee	IKARIA, INC.
Group Art Unit	1616
Examiner	ARNOLD, ERNST V.
Attorney Docket Number	I001-0002USC1

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

DECLARATION OF DAVID L. WESSEL, M.D.
UNDER 37 C.F.R. § 1.132

I, David L. Wessel, do hereby declare the following:

1. I currently hold the position of Senior Vice President, The Center for Hospital-based Specialties, at Children's National Medical Center in Washington, D.C., where I am also the Division Chief of Critical Care Medicine. I am also the Ikaria Distinguished Professor of Critical Care Medicine. A copy of my *curriculum vitae* is attached as **Exhibit 1**.

2. I received a bachelor's degree (B.S.) in physics from the College of William and Mary in 1972, a bachelor's degree (B.A.) in physiology from Oxford University in 1974, a doctoral degree (*cum laude*) in medicine (M.D.) from the Yale University School of Medicine in 1978, and a master's degree (M.A.) in physiology from Oxford University in 1983.

3. Following my graduation from Yale, the majority of my time as a practicing physician was spent in academic medicine, where I focused on pediatric cardiology. From 1978-1981, I performed an internship in pediatrics followed by a clinical fellowship at the Yale University School of Medicine. From 1981-1985, I was a fellow in pediatric anesthesiology at

Harvard Medical School, where I later became an instructor (1985), assistant professor (1987), associate professor (1994), and ultimately professor (2002), all in the area of pediatrics. In 2011, I will become a professor of pediatrics at the George Washington University School of Medicine and Health Sciences in Washington, DC.

4. In addition to my academic experience, I have extensive experience in the pharmaceutical industry as a member of scientific advisory boards, advisory panels or steering committees for companies such as Pfizer, Johnson & Johnson, Eli Lilly, Bristol-Myers Squibb, Sanofi-Avenits, and INO Therapeutics.[1]

5. In 2005, I chaired the Steering Committee of the Sponsor, INO Therapeutics LLC (INOT), to establish, design and oversee the INOT22 Study. In addition to being the Chair of the INOT22 Steering Committee, I also am the senior author of Atz and Wessel, *Seminars in Perinatology* 1997, 21(5), pp. 441-455 (Atz et al.).

6. At the time of the design of the INOT22 Study protocol, neither I, the other Steering Committee members, nor the study Sponsor appreciated or anticipated that a child with left ventricular dysfunction who is not dependent on right-to-left shunting of blood would be at additional risk when treated with inhaled nitric oxide (iNO). This is the reason such children were not originally excluded from the INOT22 Study entry criteria.

7. Neither the Atz et al. article that I co-authored, nor the medical literature or medical experience of which I was aware at the time, predict this risk. Instead, Atz et al. describes two distinct, independent precautions with respect to the use of iNO. First, with respect to adults, Atz et al. stated that iNO may be more effective in newborns than in older patients, and noted that it should be used with caution in adults with ischemic cardiomyopathy in whom a risk of pulmonary edema is a consideration (see page 452, left column). Second, with respect to neonates, we stated the well-known contraindication (currently found in the INOMAX®

[1] In the interest of full disclosure, I formerly served as a consultant for INO Therapeutics LLC. I currently serve without remuneration as a member of the Ikaria Scientific Board of Advisors. In 2010, I was appointed by my institution as the Ikaria Distinguished Professor of Critical Care Medicine.

prescribing information) that iNO should not be used in newborns dependent upon right-to-left shunting of blood across a patent ductus arteriosus to avoid circulatory collapse. What we did **not** disclose or predict was that neonatal patients with left ventricular dysfunction who are not dependent on right-to-left shunting of blood would be at greater risk of adverse events.

8. It is ironic that my own publication would be cited to suggest that it would have been obvious to predict the adverse events and outcomes of the INOT22 Study when I, the senior author of Atz et al., failed to anticipate or predict these unexpected outcomes at the time I participated in drafting the original INOT22 Study protocol. If so, I would have been acting either negligently or intentionally to harm babies, and I most certainly was not. Furthermore, to my knowledge, none of the other members of the INOT22 Steering Committee who assisted me in designing the study, nor the approximately 18 Institutional Review Boards and 2 National Health Authorities who reviewed and approved the study prior to its initiation, predicted the adverse events in children with left ventricular dysfunction who are not dependent on right-to-left shunting of blood.

9. In summary, although it was known that neonates dependent on right-to-left shunt should not receive iNO and it had been reported that adults with pre-existing left ventricular dysfunction may be at risk when provided iNO, it was unanticipated and surprising that children with left ventricular dysfunction who are not dependent on right-to-left shunting would be at increased risk of adverse events when administered iNO.

10. 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 the '359 patent.

Dated: July 15 2015

David L. Wessel, M.D.

EXHIBIT 8

TO THE DECLARATION OF GEOFFREY L. ROSENTHAL, M.D. PH.D.

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) gas, for inhalation
Initial U.S. Approval: 1999

----------RECENT MAJOR CHANGES----------
Dosage and Administration (2.2) 10/2015

---------- INDICATIONS AND USAGE----------
INOmax is a vasodilator indicated to improve oxygenation and reduce the need for extracorporeal membrane oxygenation in term and near-term (>34 weeks gestation) neonates with hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension in conjunction with ventilatory support and other appropriate agents.

----------DOSAGE AND ADMINISTRATION ----------
The recommended dose is 20 ppm, maintained for up to 14 days or until the underlying oxygen desaturation has resolved (2.1).
Doses greater than 20 ppm are not recommended (2.1, 5.2)
Administration:

- Use only with an INOmax $DS_{IR}^{®}$operated by trained personnel (2.2)
- Avoid abrupt discontinuation (2.2, 5 1).

---------- DOSAGE FORMS AND STRENGTHS----------
INOmax (nitric oxide) is a gas available in an 800 ppm concentration (3).

---------- CONTRAINDICATIONS ----------
Neonates 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: Monitor NO_2 levels (5.3).
Heart Failure: In patients with pre-existing left ventricular dysfunction, INOmax may increase pulmonary capillary wedge pressure leading to pulmonary edema (5.4).

---------- ADVERSE REACTIONS ----------
The most common adverse reaction is 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 compounds may increase the risk of developing methemoglobinemia (7).

Revised: 10/2015

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

INOmax® is indicated to improve oxygenation and reduce the need for extracorporeal membrane oxygenation in term and near-term (>34 weeks gestation) neonates with hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension in conjunction with ventilatory support and other appropriate agents.

2 DOSAGE AND ADMINISTRATION

2.1 Dosage

Term and near-term neonates with hypoxic respiratory failure

The recommended dose of INOmax is 20 ppm. Maintain treatment up to 14 days or until the underlying oxygen desaturation has resolved and the neonate is ready to be weaned from INOmax therapy.

Doses greater than 20 ppm are not recommended *[see Warnings and Precautions (5.2)]*.

2.2 Administration

Training in Administration

The user of INOmax and Nitric Oxide Delivery Systems must satisfactorily complete a comprehensive periodic training program for health care professionals provided by the delivery system and drug manufacturers. Health professional staff that administers nitric oxide therapy have access to supplier-provided 24 hour/365 days per year technical support on the delivery and administration of INOmax at 1-877-566-9466.

Nitric Oxide Delivery Systems

INOmax must be administered using a calibrated INOmax DS_{IR}® Nitric Oxide Delivery System. Only validated ventilator systems should be used in conjunction with INOmax. Consult the Nitric Oxide Delivery System label or call 877.566.9466/visit inomax.com for a current list of validated systems.

Keep available a backup battery power supply and an independent reserve nitric oxide delivery system to address power and system failures.

Monitoring

Measure methemoglobin within 4-8 hours after initiation of treatment with INOmax and periodically throughout treatment *[see Warnings and Precautions (5.2)]*.

Monitor for PaO_2 and inspired NO_2 during INOmax administration *[see Warnings and Precautions 5.3)]*.

Weaning and Discontinuation

Avoid abrupt discontinuation of INOmax *[see Warnings and Precautions (5.1)]*. To wean INOmax, downtitrate in several steps, pausing several hours at each step to monitor for hypoxemia.

3 DOSAGE FORMS AND STRENGTHS

INOmax (nitric oxide) gas is available in an 800 ppm concentration.

4 CONTRAINDICATIONS

INOmax is contraindicated in neonates dependent on right-to-left shunting of blood.

5 WARNINGS AND PRECAUTIONS

5.1 Rebound Pulmonary Hypertension Syndrome following Abrupt Discontinuation

Wean from INOmax *[see Dosage and Administration (2.2)]*. Abrupt discontinuation of INOmax may lead to worsening oxygenation and increasing pulmonary artery pressure, i.e., Rebound Pulmonary Hypertension Syndrome. Signs and symptoms of Rebound Pulmonary Hypertension Syndrome include hypoxemia, systemic hypotension, bradycardia, and decreased cardiac output. If Rebound Pulmonary Hypertension occurs, reinstate INOmax therapy immediately.

5.2 Hypoxemia from Methemoglobinemia

Nitric oxide combines with hemoglobin to form methemoglobin, which does not transport oxygen. Methemoglobin levels increase with the dose of INOmax; it can take 8 hours or more before steady-state methemoglobin levels are attained. Monitor methemoglobin and adjust the dose of INOmax to optimize oxygenation.

If methemoglobin levels do not resolve with decrease in dose or discontinuation of INOmax, additional therapy may be warranted to treat methemoglobinemia *[see Overdosage (10)]*.

5.3 Airway Injury from Nitrogen Dioxide

Nitrogen dioxide (NO_2) forms in gas mixtures containing NO and O_2. Nitrogen dioxide may cause airway inflammation and damage to lung tissues.

If there is an unexpected change in NO_2 concentration, or if the NO_2 concentration reaches 3 ppm when measured in the breathing circuit, then the delivery system should be assessed in accordance with the Nitric Oxide Delivery System O&M Manual troubleshooting section, and the NO_2 analyzer should be recalibrated. The dose of INOmax and/or FiO_2 should be adjusted as appropriate.

5.4 Worsening Heart Failure

Patients with left ventricular dysfunction treated with INOmax may experience pulmonary edema, increased pulmonary capillary wedge pressure, worsening of left ventricular dysfunction, systemic hypotension, bradycardia and cardiac arrest. Discontinue INOmax while providing symptomatic care.

6 ADVERSE REACTIONS

The following adverse reactions are discussed elsewhere in the label;

Hypoxemia *[see Warnings and Precautions (5.2)]*
Worsening Heart Failure *[see Warnings and Precautions (5.4)]*

6.1 Clinical Trials Experience

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.

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.

In CINRGI, the only adverse reaction (>2% higher incidence on INOmax than on placebo) was hypotension (14% vs. 11%).

6.2 Post-Marketing Experience

Post marketing reports of accidental exposure to nitric oxide for inhalation in hospital staff has been associated with chest discomfort, dizziness, dry throat, dyspnea, and headache.

7 DRUG INTERACTIONS

7.1 Nitric Oxide Donor Agents

Nitric oxide donor agents such as prilocaine, sodium nitroprusside and nitroglycerine may increase the risk of developing methemoglobinemia.

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 indicated for use in adults.

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

The safety and efficacy of nitric oxide for inhalation has been demonstrated in term and near-term neonates with hypoxic respiratory failure associated with evidence of pulmonary hypertension *[see Clinical Studies (14.1)]*. Additional studies conducted in premature neonates for the prevention of bronchopulmonary dysplasia have not demonstrated substantial evidence of efficacy *[see Clinical Studies (14.3)]*. 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 is manifest by elevations in methemoglobin and pulmonary toxicities associated with inspired NO_2. Elevated NO_2 may cause acute lung injury. Elevations in methemoglobin 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). 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 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.

Absorption and Distribution

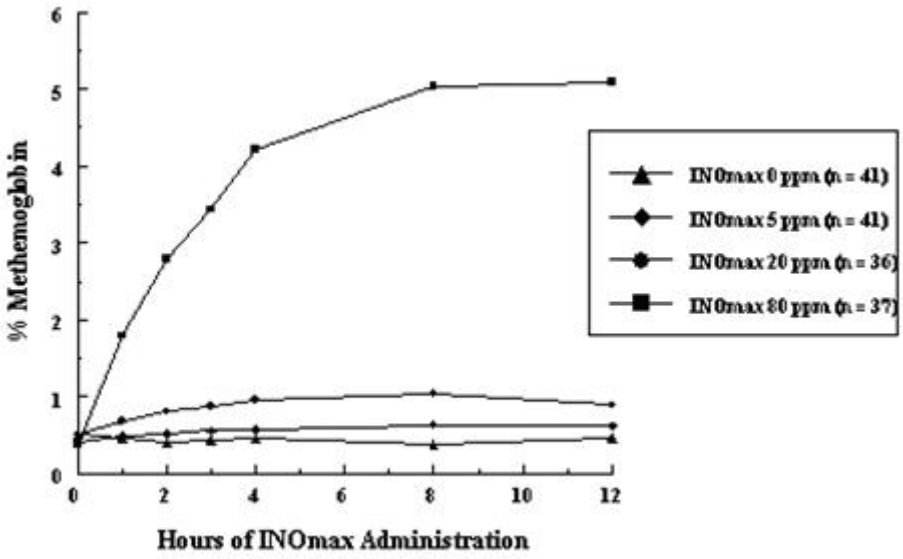
Nitric oxide is absorbed systemically after inhalation. Most of it traverses the pulmonary capillary bed where it combines with hemoglobin that is 60% to 100% oxygen-saturated. At this level of oxygen saturation, nitric oxide combines predominantly with oxyhemoglobin to produce methemoglobin and nitrate. 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.

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) was 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 (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 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 (6.1)]*.

In clinical trials, reduction in the need for ECMO has not been demonstrated with the use of inhaled nitric oxide in neonates with congenital diaphragmatic hernia (CDH).

14.2 Ineffective in Adult Respiratory Distress Syndrome (ARDS)

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.

14.3 Ineffective in Prevention of Bronchopulmonary Dysplasia (BPD)

The safety and efficacy of INOmax for the prevention of chronic lung disease [bronchopulmonary dysplasia, (BPD)] in neonates ≤ 34 weeks gestational age requiring respiratory support has been studied in four large, multi-center, double-blind, placebo-controlled clinical trials in a total of 2,600 preterm infants. Of these, 1,290 received placebo, and 1,310 received inhaled nitric oxide at doses ranging from 5-20 ppm, for treatment periods of 7-24 days duration. The primary endpoint for these studies was alive and without BPD at 36 weeks postmenstrual age (PMA). The need for supplemental oxygen at 36 weeks PMA served as a surrogate endpoint for the presence of BPD. Overall, efficacy for the prevention of bronchopulmonary dysplasia in preterm infants was not established. There were no meaningful differences between treatment groups with regard to overall deaths, methemoglobin levels, or adverse events commonly observed in premature infants, including intraventricular hemorrhage, patent ductus arteriosus, pulmonary hemorrhage, and retinopathy of prematurity.

The use of INOmax for prevention of BPD in preterm neonates ≤ 34 weeks gestational age is not recommended.

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 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)

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

All regulations concerning handling of pressure vessels must be followed.

Protect the cylinders from shocks, falls, oxidizing and flammable materials, moisture, and sources of heat or ignition.

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.

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EXHIBIT 9

TO THE DECLARATION OF GEOFFREY L. ROSENTHAL, M.D. PH.D.

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EDITORIAL

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Towards rational use of inhaled Nitric Oxide in preterm babies

On the basis of best available evidence, learned authorities do not recommend routine use of inhaled nitric oxide (iNO) in preterm infants in hypoxic respiratory failure (1). Yet published audits, mainly from resource rich health systems, show that iNO continues to be used in a significant minority of very preterm infants, in increasing proportions in the most immature (2,3). The forces that drive this usage are probably the intensivist's instinct to try everything when approaching the end of the therapeutic line in a baby with failing oxygenation. This is understandable, but iNO is an expensive treatment, and no health system has infinite resources, so the continuing widespread use in preterm infants is cause for concern, review and rationalisation.

Implementation of findings from clinical trials into practice should always be cognisant of the generalisability. Most of the clinical trials of INO in preterm infants for hypoxic respiratory failure, enrolled on the basis of oxygenation alone, usually oxygenation index (OI). These trials did enrol on the basis of range of severe OIs and included a range of gestations and birthweights. So the evidence is clear that if you are faced with a preterm baby in whom the only information you have in relation to pulmonary hypertension (PH) is a high OI, then administration of iNO will not generally improve this baby's outcome. But questions remain as to whether this generalisation applies all preterm babies.

In this edition of Acta Paediatrica, the study of Cheng et al. (4) highlights some of the unanswered questions around the use of iNO in the very preterm infant. iNO is a vasodilator that relieves pulmonary vasoconstriction in PH. Yet none of the clinical trials used an assessment for PH in the enrolment criteria. Instead, they made the pragmatic but flawed assumption that oxygenation is a surrogate marker for PH. Not all babies with oxygenation failure have PH and not all babies with PH have oxygenation failure (5). Cheng et al. ask the important question whether introduction of neonatologist performed cardiac ultrasound (NPCU) into their programme, and so more accurate assessment of pulmonary artery pressure (PAP), had changed the pattern of usage and outcome of iNO in preterm infants. The study is limited by its retrospective design, and incomplete ultrasound assessment of babies in the period after ultrasound was introduced, only 64% had an ultrasound assessment. After introduction of NPCU, iNO was used in more preterm babies and it was used earlier (median 1.8 hours) and for shorter duration, but there was no differences in other outcomes. It is difficult to interpret from this data whether introduction of NPCU led to a rationalisation of the use of iNO, particularly as the numbers increased in the later ultrasound epoch. It is possible that the ultrasound findings encouraged more treatment with iNO. The paper does not give us the population denominator in each time epoch to allow interpretation of this.

The evidence from clinical trials is not only confounded by a lack of assessment of PAP but also a continuation of two misconceptions in the design of those trials; firstly, that PH is a common primary problem in preterm respiratory disease and secondly that neonatal PH represents just one haemodynamic, that of high pulmonary vascular resistance with reduced pulmonary blood flow, and right to left shunt through the foetal channels, the classic persistent foetal circulation. Nothing is simple in biological systems and many factors play into preterm PAP. Firstly, the natural fall in PAP during the postnatal period is slower than many imagine. Even in well-term babies, it is not uncommon to find pulmonary pressures close to systemic for the first six to eight hours of life (6). Some of this is due to overshoot of the natal increase in pulmonary blood flow as a result of left to right shunt through the ductus before closure. The laws of fluid dynamics dictate that pulmonary pressure is the product of resistance and flow. Postnatally, resistance falls and flow rises so pressures stay much the same. This increase in blood flow is often exaggerated in the preterm infant with failure of ductal constriction. The second is that positive pressure ventilation in itself will increase PAP, particularly at higher ventilation pressures. PAP has to be higher in this situation to maintain pulmonary blood flow in the face of high positive intrathoracic pressure. So when using ultrasound to assess for PH in a two-hour-old baby on high-pressure ventilation, defining pathological from physiological can be difficult. What is clear is that it should be more than just a measure of PAP. In both circulations, pressure is only important in as much as how it reflects in flow.

iNO is associated with a wide range of response in terms of improvement in oxygenation. At one end of the spectrum, there is no (or muted) change; at the other end, a baby will go from 100% oxygen to air in a matter of minutes.

There is relatively little work defining the preceding haemodynamic basis for this spectrum of response but two papers, both from France, showed an inverse relationship between blood velocity in the left pulmonary artery and improvement in oxygenation (7,8). The authors argue that low LPA velocity is a marker of low pulmonary blood flow due to vasoconstriction being a primary pathological problem. This, in turn, would identify babies in whom a pure vasodilator, such as iNO, will likely increase pulmonary blood flow and so oxygenation. Experientially, low pulmonary blood flow PH is not common in preterm babies, and most have high pulmonary blood flow PH in the presence of a ductal shunt. From early after birth, the dominant direction of ductal shunting, even when the pattern is bidirectional, is left to right. The group in whom one does observe the low pulmonary blood flow PH haemodynamic most consistently are those born after prolonged preterm rupture of membranes and oligohydramnios. Several observational reports in the literature have described this group of babies as likely to show a brisk improvement in oxygenation (and ventilation needs) with iNO (9). My clinical experience is consistent with this, and this would be a group of preterm babies with hypoxic respiratory failure in whom I would use iNO once I had confirmed the haemodynamic with ultrasound. They often improve dramatically. Oligohydramnios babies are not common so I rarely use iNO in preterm babies.

So how to rationalise this usage and how to develop an evidence base around the above, which is largely observational and experiential. It needs to be recognised that not all preterm babies with hypoxic respiratory failure have the same underlying haemodynamic pathology and so they are unlikely to all respond to the same treatment. I agree with Cheng et al., that the answer will probably lie in an approach that includes haemodynamic ultrasound assessment, as well as recognition of and earlier use in babies most likely to benefit. In preterm neonatology, it is invariably better to prevent than to rescue. Such an individualised approach does not lend itself well to the conventional 'one size fits all' design of a clinical trial. It is clear that the available evidence does not support the current incidence of usage being described in the literature, but whether more widespread usage of haemodynamic ultrasound assessment will rationalise this will depend on a tighter definition of what is pathological. I would propose that this definition should include a PAP that is at or above a normal systemic blood pressure as well as markers of low pulmonary blood flow. This would better define babies in whom it is high resistance not high flow which is driving the PH. If treatment is administered only on the basis of a PAP above normal, this will encompass most babies on ventilators in the early hours after birth and such ultrasound assessments may actually increase usage.

CONFLICT OF INTEREST

The author has no conflicts of interest to declare.

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EXHIBIT 10

TO THE DECLARATION OF GEOFFREY L. ROSENTHAL, M.D. PH.D.

Prolonged Rupture of Membranes and Pulmonary Hypoplasia in Very Preterm Infants: Pathophysiology and Guided Treatment

Koert de Waal, PhD[1], and Martin Kluckow, PhD[2]

Preterm premature rupture of the fetal membranes (PPROM) with loss of amniotic fluid in the second trimester is associated with high perinatal mortality and can cause major neonatal morbidity. Premature rupture of membranes complicates up to 3% of all pregnancies, with 0.4% of ruptures occurring before or near the limit of viability.[1] Approximately one-half of the pregnancies will deliver within 1 week after the membranes rupture and up to 70% within 5 weeks. Besides extreme prematurity and sepsis, hypoxic respiratory failure attributable to presumed pulmonary hypoplasia is a major contributor to the quoted high mortality of infants born after PPROM.

Prospective risk assessment after PPROM in the second trimester remains difficult. Antenatal counseling generally has been negative, particularly with PPROM before 20 weeks' gestation. This subgroup is of concern, as it has the greatest quoted mortality and morbidity. Systematic reviews summarizing the data up to the year 2000 reported an average perinatal survival rate of 18% and a neonatal survival rate around 50%.[2,3] However, more recent data have reported a neonatal survival of greater than 70% as the result of improved antenatal surveillance and new postnatal treatment strategies.[4-6] Survival occurs despite severe initial respiratory failure,[7] and short- and long-term neonatal outcomes are approaching those of matched gestational-age infants.[4,8] Changes in the approach to PPROM and suspected pulmonary hypoplasia include a tailored approach toward mechanical ventilation, use of serial cardiac ultrasound (often performed by the clinician caring for the infant), and early use of inhaled nitric oxide (iNO). We present an overview of the pathophysiologic changes in the lung that can occur with PPROM, which can affect the transition from fetal life to newborn. On the basis of the available evidence, we propose that targeted clinical management based on the underlying pathophysiology is a logical approach in this subgroup of preterm infants with hypoxic respiratory failure.

Pathophysiologic Changes after PPROM

An understanding of the unique pathophysiology of infants affected by PPROM is an essential step to planning appropriate and timely therapy and consequently improving outcomes after PPROM. Absence or severe reduction in the volume of the amniotic fluid results in the abnormal development of both the lung parenchyma and the pulmonary vasculature.

iNO	Inhaled nitric oxide
PPROM	Preterm premature rupture of the fetal membranes

Lung Pathophysiology

Postmortem studies in humans show that most preterm infants who die from hypoxic failure after PPROM have significantly lower lung weights and lung volumes.[9,10] There is impaired morphologic maturation of the lung in PPROM with reduced airspaces and elastin but a normal amount of type II cells and normal phospholipid concentrations similar to that found in animal studies.[11] Studies in animals recreating oligohydramnios show a variety of changes in the lung. Pulmonary hypoplasia was the main feature with an added component of reduction in chest wall compliance.[12,13] Clinically, newborn animals show reduced tidal volume with increased respiratory frequency, but with normal minute ventilation. In a PPROM sheep model with a latency period of 35 days and preterm delivery at 95% of term,[14] lung weight and lung compliance were significantly smaller in the animals with pulmonary hypoplasia compared with controls. Ventilator indices, such as measures of efficiency of CO_2 elimination and total respiratory system compliance, also were reduced.

Cardiovascular Pathophysiology

The pulmonary circulation of lambs with hypoplastic lungs had a significantly increased pulmonary vascular resistance with high pulmonary artery pressure and reduced pulmonary blood flow.[14] Importantly, when expressed per kilogram of lung weight, Suzuki et al[14] found that the changes in indices of lung ventilation were proportional to the changes in lung size, and that the changes in indices of the pulmonary circulation were greater than the changes in lung size. All respiratory and hemodynamic effects of pulmonary hypoplasia were most pronounced in the first 60 minutes after birth, providing a window of opportunity for treatment of the reversible hemodynamic elements of the pathophysiology. Histologic changes of the pulmonary vasculature include reduced volume density of pulmonary arteries and increased acinar arterial wall muscle thickness.[15]

Increased Pulmonary Vascular Pressure

The characteristic transitional hemodynamic changes in preterm infants with hypoxic failure born after PPROM in the

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second trimester include a varying degree of pulmonary hypertension, either diagnosed clinically or with echocardiography. Pulmonary hypertension during the transition describes a situation in which the pulmonary pressure is greater than the systemic pressure, leading to shunting of blood away from the lungs. Different pathophysiologic elements contribute to pulmonary hypertension, including high pulmonary vascular resistance, the degree of pulmonary parenchymal disease, the presence of myocardial damage due to hypoxia, impaired right ventricular function, variability in vasoactive tone and systemic blood pressure due to inflammation, the size and patency of fetal shunts, and heart-lung interactions. All elements can interact with each other to produce the overall clinical picture of pulmonary hypertension with hypoxic failure.

In a PPROM case series, hemodynamic measurements in the first 24 hours after birth showed a pure right-to-left shunt through the ductus arteriosus indicating that pulmonary pressure exceeded the systemic pressure throughout the cardiac cycle in 5 of the 6 infants with severe hypoxic failure.[16] This "true" persistent fetal circulation early after birth is also our local experience. In our local cohort of 7 infants with severe hypoxic failure after PPROM, systemic blood pressure initially was normal. Cardiac ultrasound scans within 2 hours after birth showed a low left ventricular output due to low preload of the left ventricle, a low to normal right ventricular output, a normal flow in the superior vena cava, and a pure right-to-left shunt over the ductus arteriosus in 6 of the 7 patients (data not shown). With the right-to-left shunting, the ductus arteriosus is adding blood flow to the low left ventricular output, supporting the lower one-half of the body with extra blood of mixed saturation. If the hypoxia does not improve or if it is severe enough to cause acidosis, pulmonary vascular resistance will increase further. The systemic blood pressure and blood flow will decrease, entering a spiral downwards with further increases in the pulmonary to systemic pressure ratio and more shunting bypassing the alveoli of the lung, ending in fatal hypoxic failure.

If a clinical balance is achieved with adequate oxygen saturation and pH, persistent high pulmonary pressures can complicate the clinical picture during the course of the disease. With ductal constriction, which will almost invariably happen, the hemodynamic situation can change and the infant can develop right ventricular failure as the result of high afterload. This situation is comparable with infants with congenital diaphragmatic hernia after ductal closure[17] or adults with severe pulmonary hypertension.[18]

Management of Infants with PPROM Based on Physiology

The elements of the pathophysiology of infants born after PPROM include small lungs with relative normal compliance, a very high pulmonary vascular resistance with reduced pulmonary blood flow, and often a degree of systolic and diastolic cardiac dysfunction. Treatment in the first hours after birth should be aimed at titrating optimal lung distension with low volumes, thus avoiding overdistention and managing high pulmonary vascular resistance. The pulmonary vascular changes often are more pronounced than the parenchymal changes in infants with severe hypoxic failure, and it is important to find the right respiratory and cardiovascular balance early in the disease process.

The Respiratory Component of PPROM

Physiology and Respiratory Approach

The common physiology of small lungs with relatively normal compliance suggests an approach with low distending pressures to achieve optimal distention without causing excessive intrathoracic pressures that can affect the preload and afterload of the heart. A low-volume ventilation strategy should be titrated to lung size, not to body size. Dargaville and Tingay[19] suggest a low-pressure strategy and avoidance of lung recruitment unless the lung parenchyma is opacified on chest radiographs. Consistent with other authors, they suggest an early transition to high-frequency oscillatory ventilation if hypoxia does not improve with conventional ventilation.[20,21] The importance of overdistention as a key factor leading to death in preterm infants with pulmonary hypoplasia is emphasized. With low compliant lungs, as is found in preterm infants with respiratory distress syndrome, very high distending pressures will only minimally reduce right ventricular output.[22] If lung compliance is relatively normal, as is found in hypoplastic lungs, small increases in end expiratory pressure and/or mean airway pressure can significantly reduce venous return and cardiac output, worsening the cardiovascular component of the clinical picture.

Other Respiratory Management

Although studies in animals do not indicate delayed maturation of surfactant production after PPROM, no clear evidence on surfactant use is available from the literature. Early surfactant is recommended by most authors to stay a step ahead of the added effects of respiratory distress syndrome in a population in which the incidence of surfactant deficiency is high. Arterial blood gas targets are based on the known physiological response of the pulmonary vasculature to PaO_2 and $PaCO_2$. Hypoxic pulmonary vasoconstriction is increased at PaO_2 levels less than 50 mm Hg, hence the target PaO_2 should remain above this level.[23] The target for $PaCO_2$ is less clear. Recent investigations into the effect of CO_2 on the pulmonary circulation are conflicting. It seems CO_2-related changes to the pulmonary vascular tone differ between the normal and injured lung, and they vary depending on pulmonary pressures and the presence of endogenous nitric oxide.[24] Of importance, the effect of hypoxia on the pulmonary vasculature is more pronounced than any effect of pH and/or CO_2. However, acidosis can modulate the pulmonary vasoconstrictive effects of hypoxia.[25] In congenital

diaphragmatic hernia, a comparable situation of pulmonary hypoplasia and severe hypoxia, respiratory strategies that include permissive hypercapnia to allow for lower ventilator pressures have led to improved clinical outcomes.[26]

Supportive Management

Sedation and sometimes paralysis are recommended by some authors to counteract the effect of spontaneous ventilation.[4,19] We do not recommend routine paralysis in preterm infants with PPROM. Data on use of routine paralysis stem from the era before surfactant was available and did not show any pulmonary benefits.[27] Side effects of pancuronium include vagal blockade and catecholamine and histamine release. There are no immediate cardiovascular effects of vecuronium, but continuous use of paralyzing agents will alter venous capacitance and risk destabilizing the cardiovascular balance.[28] In a systematic literature review in which the authors explored supportive treatment for the similar physiology of congenital diaphragmatic hernia, a trend was noted towards more use of narcotic analgesia and avoidance of paralysis with improved clinical outcomes.[29] There seems to be a general beneficial effect of spontaneous respiration on clinical outcomes in preterm infants, including in the management of infants with pulmonary hypoplasia secondary to PPROM. Welzing et al[30] successfully used early nasal continuous positive airway pressure and iNO in 7 PPROM-affected preterm infants and hypoxic failure, with only one patient needing mechanical ventilation.

The Cardiovascular Component of PPROM

Physiology

There is individual variation in the degree of pulmonary hypertension and the underlying pathophysiologic elements. Because of its complexity, Geary and Whitsett[31] describe this situation as clinicians find themselves responding to, rather than staying a step ahead of, the clinical problems. The clinical response to hypoxic failure is often to increase the ventilator pressures, but frequently not with the desired response. It is difficult to distinguish the parenchymal and vascular component of the hypoxia without detailed insight into the degree of extrapulmonary shunting, intracardiac volume status and left and right ventricular function and outputs.

The most distinguishing hemodynamic feature in infants with severe hypoxia after PROM is a pulmonary to systemic pressure imbalance. A pure ductal right-to-left shunt is rare in newborn infants with significant hypoxic respiratory failure and a normal cardiac structure.[32,33] The differential diagnosis includes severe systemic hypotension with normal pulmonary pressure,[34] very high intrathoracic pressure (eg, tension pneumothorax),[35] and infants with pulmonary hypoplasia due to other causes such as in congenital diaphragmatic hernia.[36] Early treatment of high pulmonary pressure, via the use of the degree of right-to-left shunting through the ductus arteriosus as a diagnostic feature, assists in avoiding overdistention as the result of increasing ventilator pressures in response to persisting hypoxia. Increasing ventilator pressures is an effective clinical approach to hypoxia if it is caused by pulmonary parenchymal changes with low compliant lungs but not effective if the majority of the hypoxia is attributed to a pulmonary to systemic pressure imbalance and a wide open ductus arteriosus. Changing the pulmonary pressure early in the disease process has the potential to alter the clinical course, minimizing lung damage and pulmonary complications.

Diagnosis

Early and serial cardiac ultrasound is ideal to classify the physiology, target therapy, and monitor responses in this group of infants.[16,20,21] The pathophysiology of pulmonary hypoplasia is characterized by a very high pulmonary vascular resistance, high pulmonary pressure, and low pulmonary blood flow. A pure right-to-left shunt over the ductus arteriosus can be used to diagnose this hemodynamic pattern. With ultrasonography, a probe should be placed in the left high parasternal area to visualize the pulmonary trunk, the ductus arteriosus, and the aorta in 1 view (**Figure 1**). When color Doppler is added to the image, it will show blood flow away from the probe (tagged blue) towards the descending aorta in all 3 vessels (**Figure 2**, A). Pulse-wave Doppler analysis of the waveform in the ductus arteriosus will be predominantly directed downwards (**Figure 2**, B). When the pulmonary pressure is lower than the systemic pressure, the color Doppler pattern is red in the ductus arteriosus, indicating blood flowing towards the probe and towards the pulmonary trunk, and blue in the pulmonary trunk and aorta (**Figure 2**, C). Most of the flow velocity is directed upwards on pulse wave analysis (**Figure 2**, D). This strong contrast in color makes bedside diagnosis of right-to-left shunt easy in the early postnatal phase, where the duct is wide open. Similarly, reversal of these changes with treatment is also relatively easy to document. The frequency and interval of cardiac ultrasounds will depend on clinical response. An ultrasound before and after each intervention is recommended to assess whether the desired changes in physiology have occurred.[37]

Use of iNO and Other Pulmonary Vasodilators

After establishing the diagnosis of high pulmonary pressure and its underlying pathophysiologic elements, treatment should be directed at the findings. As opposed to the pulmonary parenchymal changes, the hemodynamic effects of the vascular changes often are reversible. Treatment includes lowering the pulmonary pressure and supporting the systemic circulation. In preterm infants with severe hypoxia and high pulmonary pressure after PPROM, iNO is the most studied drug to help reduce pulmonary pressure and improve oxygenation. It does this by both inducing pulmonary vasodilation as well as improving the common ventilation perfusion mismatch by virtue of the route of delivery.[38] **Table I**[5,7,16,30,31,39–42] summarizes the studies providing details of infants born after PPROM in which early iNO

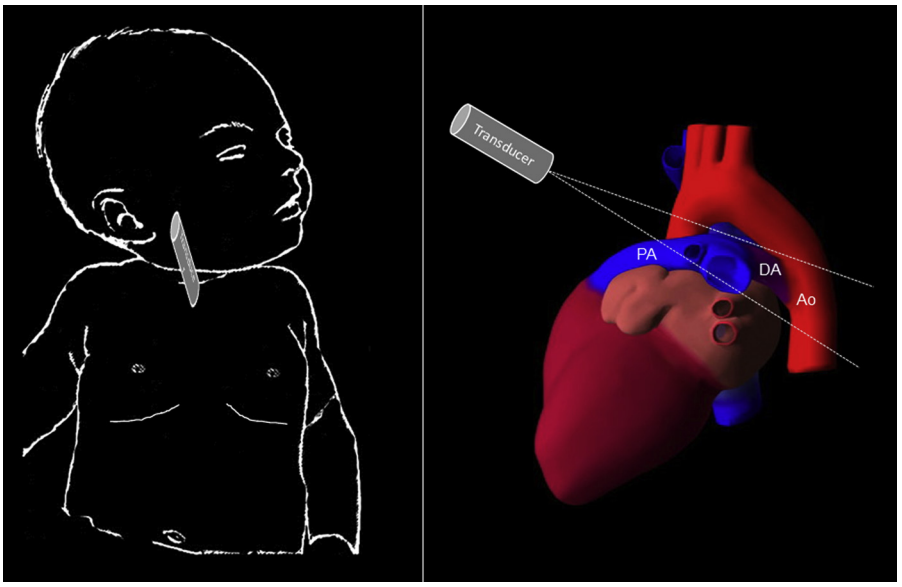

Figure 1. High parasternal position of the ultrasound probe on the chest of a newborn for imaging the pulmonary artery trunk (PA), ductus arteriosus (DA), and aortic arch (Ao) in one view (*left*) and a schematic representation of the cardiac anatomy (*right*). Adapted with permission from: Evans N. Practical echocardiography for the neonatologist (CD-ROM), developed by Evans N, Malcolm G. Sydney: Royal Prince Alfred Hospital; 2006.

was used. After establishing the diagnosis of high pulmonary pressure, usually with cardiac ultrasound early in the disease process, iNO improved oxygenation in 94% of the cases and provided the ability to wean mean airway pressure, with overall survival greater as previously described. The efficacy of early iNO in this targeted population is high compared with iNO use in the general preterm population with respiratory failure, possibly explained by a temporary disturbance of endogenous nitric oxide availability in preterm infants born after PPROM.[39] We acknowledge the possibility of publication bias with these mostly small case series, but the summary results are the best available evidence thus far.

Alternatives and/or adjuncts to iNO therapy such as phosphodiesterase inhibitors (sildenafil, milrinone), prostaglandin analogues (iloprost), magnesium sulfate, endothelin receptor antagonists, and adenosine have all been used successfully in term newborn infants with pulmonary hypertension.[43] Several of these alternatives are only studied in term infants, and the risks of use in sick preterm infants are not well understood. As with iNO, targeted treatment based on pathophysiologic findings may well prove beneficial,[44] but further reports of use in preterm infants with PPROM are needed.

Other Cardiovascular Support

Cardiovascular support often is used in preterm infants with severe hypoxic failure after PPROM.[6,8,39] Systemic hypotension and reduced right and/or left ventricular function are the main indications to start cardiovascular support. The choice of support should be directed by the underlying pathophysiology with the aims of improving systemic blood pressure, supporting cardiac function, and decreasing pulmonary pressure, or at least not increasing pulmonary pressure. This may prove to be difficult, because most pressors can cause an increase in both the systemic and pulmonary pressure, changing the relative pressure ratio between the pulmonary and systemic circulations. Similarly, inodilators can cause systemic hypotension exacerbating any right to left ductal shunting already present.

Suggestions for cardiovascular support and its effects are summarized in **Table II**.[45-52] Continuous arterial blood pressure monitoring and frequent ultrasound assessment of cardiac function are essential to guide further treatment, but it remains difficult to recommend absolute targets of blood pressure and blood flow for initiation and titration of cardiovascular support.[53] However, because systemic to pulmonary pressure imbalance is one of the main features of infants born after PPROM, low systemic blood pressure can be detrimental to pulmonary blood flow. In contrast, increasing inotropic support until so-called suprasystemic pressures are reached is also not recommended, because it will commonly increase the pulmonary pressure as well. In addition too much inotrope can negatively affect cardiac function.[54] Replacing one supportive treatment for another instead of adding them together could be considered to prevent catecholamine overload.

Severe left ventricular systolic dysfunction with increased left atrial pressure should probably be corrected before iNO is started to avoid the potential to cause pulmonary interstitial edema and worsening of oxygenation.[55]

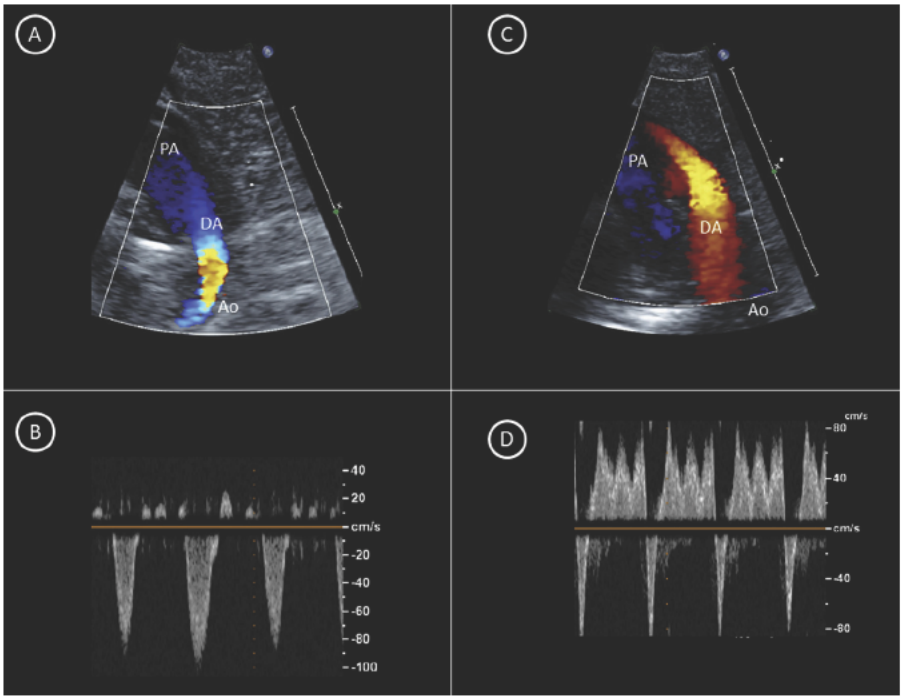

Figure 2. Left high parasternal ultrasound view of the pulmonary artery trunk (PA), ductus arteriosus (DA) and aorta (Ao) in a preterm infant with pulmonary hypertension after PPROM. **A,** Color Doppler view of pulmonary hypertension, *blue* indicating blood flowing away from the probe in all 3 vessels. **B,** Pulse-wave Doppler analysis of the waveform in the ductus arteriosus, right-to-left shunt is directed downwards. **C,** Color Doppler pattern 5 minutes after iNO was started and improved oxygenation was seen. *Red* in the ductus arteriosus indicates blood flowing towards the probe and towards the pulmonary trunk, and *blue* in the pulmonary trunk and aorta. **D,** Pulse-wave analysis now shows bidirectional flow velocity, with most of it going left-to-right, or upwards.

Improving Outcomes after PPROM

Early assessment of the hemodynamic features with delineation of the various elements of pulmonary hypertension and systemic cardiovascular adequacy, followed by targeted treatment and monitoring of treatment effect, is important in improving outcomes in PPROM. To achieve this goal, immediate and frequent access to an ultrasound machine and ultrasound skills are essential. Such a service is not always available. Most pediatric cardiologists provide a consultative service, not continuous bedside monitoring. This indicates the need for greater dissemination of ultrasound skills to bedside clinicians.[37,56] Close collaboration with the consultative specialties is needed in order to have an assessment by the pediatric cardiologist complemented by point of care ultrasound performed by bedside clinicians. Structured training and accreditation systems need to be designed to suit local health care systems, but also made

Table I. Summary of trials in which iNO was started early in preterm infants after PPROM in the second trimester

Study	Design	Treated with iNO	GA, wk	Ultrasound diagnosis of PH	Pre-iNO MAP, cmH_2O	Pre-iNO oxygenation index	Age at start iNO, h	Improved oxygenation	Survival
Peliowski et al[40]	Case series	8	24-31	5/8	12-22	25-76	2-11	8/8	5/8
Lindner et al[7]	Case series	5	24-34	Some	n/a	n/a	n/a	4/5	n/a
Geary and Whitsett[31]	Case report	2	29-31	1/2	n/a	n/a	10-24	2/2	2/2
Uga et al[41]	Case series	8	24-30	7/8	12.6 +/− 2.8	28.8 +/− 18.3	11.5 +/− 11.6	8/8	8/8
Chock et al[42]	RCT	6	24-31	2/6	n/a	11-64	12 +/− 8	5/6	4/6
Williams et al[5]	Case series	9	25-31	4/9	15-19	25-80	0.5-12	7/9	7/9
Shah and Kluckow[16]	Case series	6	26-31	6/6	13-18	23-35	6-24	6/6	6/6
Welzing et al[30]	Case series	7	28-33	Some	n/a	n/a	0.2-15	6/6	6/6
Aikio et al[39]	Cohort	17	27 +/− 2	17/17	n/a	20-70	1.5-16.5	17/17	15/17

GA, gestational age; *MAP*, mean airway pressure; *n/a*, not available; *PH*, pulmonary hypertension; *RCT*, randomized controlled trial.
Data presented as range or mean +/− SD.

Table II. Cardiovascular support agents, mechanism of action, and physiologic targets

Cardiovascular support agents	Expected actions	Comments	Physiological target
Volume	Improves cardiac input		Low preload, collapsed systemic veins
Dopamine[45,46]	Pressor	Increases afterload May increase PAP/SAP	Systemic hypotension, normal blood flow
Dobutamine[47,48]	Pressor, improves contractility	Tachycardia May decrease PAP/SAP	Low contractility, low blood flow
Epinephrine[45,46]	Pressor, improves contractility	Tachycardia Beta-adrenergic stimulation with hyperglycemia and increased lactate May decrease PAP/SAP	Low contractility, low blood flow, systemic hypotension
Norepinephrine[49,50]	Pressor, improves contractility	Increases afterload Can decrease PAP/SAP No reports in preterm infants	Low contractility, systemic hypotension
Milrinone[51,52]	Phosphodiesterase inhibitor, improves contractility	Reduces afterload Tachycardia, systemic hypotension May exacerbate right-to-left shunting	Low contractility, low blood flow, high afterload

PAP/SAP, pulmonary to systemic pressure ratio.

relevant and achievable according to the training needs of neonatologists.[57]

The clinical problem of PPROM does not easily allow for a large randomized trial design or meta-analysis to understand the benefits of the range of available treatment options. One of the difficulties in studying treatment and outcomes after PPROM is the clinical definition of pulmonary hypoplasia. It is not unique, and often overlaps with other common neonatal causes of respiratory failure.[3] Hence, alternative trial designs should be considered.[58] A web-based system or clinical register in which clinicians can enter regular respiratory, hemodynamic, and intervention data in the first 48 hours of a patient born after PPROM, documenting both the treatments used and the physiological responses to these, could provide a wealth of information in a short period of time. Variation in local management strategies could be evaluated using an interrupted time series design. This quasiexperimental research design could report on repeated observations made at regular intervals of, for example, the oxygenation index, with and without interventions (eg, iNO) or compare differing times for the intervention.[59]

An extension of this design would be an N-of-1 trial, where each patient acts as his or her own control and would be randomized to 1 or several interventions (including placebo) to determine predefined short-term effectiveness. It is important to define effectiveness with much detail, including a physiological response, so the decision to start and/or stop a certain treatment would be less influenced by the expectations of the clinician. This trial design could be effective at identifying and minimizing the time on suboptimal interventions.[60]

The most recent American Academy of Pediatrics clinical report on the use of iNO in the preterm infant does not even mention the use of iNO in PPROM-affected infants.[61] Meta-analysis of trials with variable nonphysiology based eligibility and different outcomes have led us to assume that iNO is not useful in this setting, but clearly iNO has a place if targeted to the right pathophysiological subgroup. The key lies in recognizing and diagnosing these specific subgroups, with the use of a marksman-like or targeted approach to further improve outcomes.[62] ■

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50 Years Ago in *The Journal of Pediatrics*

Pulmonary Function in Children with Pectus Excavatum

Orzalesi MM, Cook CD. J Pediatr 1965;66:898-900

Lung volumes, maximal breathing capacity, and timed vital capacity were measured in 12 children with pectus excavatum. The subjects were reported to have severe deformity, but the degree of severity was not documented. Their lung function variables were compared with that of normal children. Although vital capacity, total lung capacity, and maximal breathing capacity of the subjects were significantly reduced, all individual values were still within 2 SDs of the normal values. Five subjects underwent surgical treatment for their pectus excavatum, and repeat pulmonary function test was carried out on average 5 years after the operation. No significant change in pulmonary function could be demonstrated. The authors commented that the only justifications for surgical intervention in individuals with pectus excavatum are the possible cosmetic or psychological benefits that may result. Management of pectus excavatum has come a long way since the publication of this manuscript. Haller index, calculated as the inner transverse thoracic diameter divided by the anteroposterior distance between the anterior thoracic wall and the spine at the narrowest point, is used as a severity marker of chest wall depression. Increasing Haller index score significantly correlates with decreasing pulmonary function with a restrictive pattern.[1] Nowadays, the minimally invasive Nuss technique is the operation of choice for pectus excavatum repair. The procedure involves thoracoscopy-assisted insertion of a bar or plate behind the deformity to displace the sternum anteriorly. Recent evidence suggest a decrease in pulmonary function during the early postoperative period, however, there is a small but significant improvement during the late postoperative period and after bar removal. As for cardiac function, early improvement that is sustained during longer term follow-up has been found.[2] In addition to offering benefits to the patient's appearance and psychology, repair of pectus excavatum also improves their cardiopulmonary function, especially in those with the most severe deformity. ■

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EXHIBIT 11

TO THE DECLARATION OF GEOFFREY L. ROSENTHAL, M.D. PH.D.

Inhaled Nitric Oxide and Hypoxic Respiratory Failure in Infants With Congenital Diaphragmatic Hernia

The Neonatal Inhaled Nitric Oxide Study Group (NINOS)

ABSTRACT. *Objective.* **We designed and conducted a randomized, double-masked, controlled multicenter study to determine whether inhaled nitric oxide (INO) in term and near-term infants with congenital diaphragmatic hernia (CDH) would reduce the occurrence of death and/or the initiation of extracorporeal membrane oxygenation (ECMO).**

Patients and Methods. **Infants of 34 weeks gestation or more, <14 days of age with CDH, without known structural heart disease, requiring assisted ventilation for hypoxemic respiratory failure with two oxygenation indices (OIs) of 25 or more at least 15 minutes apart, were eligible for this trial. Infants were centrally randomized and then received masked treatment with 20 ppm NO or 100% oxygen as control. Infants with less than a full response to 20 ppm NO (increase in Pa_{O_2} >20 Torr) after 30 minutes were evaluated at 80 ppm NO/control study gas.**

Results. **The 28 control and 25 treated infants enrolled by the 13 participating centers were not significantly different at randomization for any of the measured variables including prerandomization therapies and initial OIs (45.8 ± 16.3 for controls, 44.5 ± 14.5 for INO). Death at <120 days of age or the need for ECMO occurred in 82% of control infants compared with 96% of INO infants (ns). Death occurred in 43% of controls and 48% of the INO group (ns), and ECMO treatment was used for 54% of control and 80% of INO-treated infants. There was no significant improvement in Pa_{O_2} (Δ Pa_{O_2} 7.8 ± 19.8 vs 1.1 ± 7.6 Torr, ns) nor significant reduction in OI (-2.7 ± 23.4 vs 4.0 ± 14.8, ns) associated with INO treatment. Mean peak nitrogen dioxide (NO_2) concentration was 1.9 ± 1.3 ppm and the mean peak methemoglobin was 1.6 ± 0.8 mg/dL. No infant had study gas discontinued for toxicity. There were no differences between the control and INO groups for the occurrence of intracranial hemorrhage, specific grades of intracranial hemorrhage, periventricular leukomalacia, brain infarction, and pulmonary or gastrointestinal hemorrhages.**

Conclusions. **Although the immediate short-term improvements in oxygenation seen in some treated infants may be of benefit in stabilizing responding infants for transport and initiation of ECMO, we conclude that for term and near-term infants with CDH and hypoxemic respiratory failure unresponsive to conventional therapy, inhaled NO therapy as used in this trial did not reduce the need for ECMO or death.** *Pediatrics* **1997;99:838–845;**

ABBREVIATIONS. CDH, congenital diaphragmatic hernia; HFOV, high-frequency oscillatory ventilation; ECMO, extracorporeal membrane oxygenation; NO, nitric oxide; NO_2, nitrogen dioxide; EDRF, endothelium-derived relaxing factor; INO, inhaled nitric oxide; PPHN, persistent pulmonary hypertension of the newborn; OI, oxygenation index; BPD, bronchopulmonary dysplasia; ELSO, Extracorporeal Life Support Organization; DSMC, Data Safety and Monitoring Committee; NOS, nitric oxide synthase; eNOS, endothelial NOS; neuronal NOS.

Congenital diaphragmatic hernia (CDH) is a malformation that occurs in approximately 1 in every 3000 to 4000 deliveries.[1] The overall mortality for fetuses with isolated, potentially correctable CDH diagnosed before 24 weeks gestation is approximately 58%.[2] Despite the very aggressive support required to maintain adequate gas exchange in infants with CDH who present with early-onset severe respiratory distress, there is a high rate of failure of conventional management. The major underlying pathophysiology in such infants appears to be a combination of lung hypoplasia and immaturity and persistent pulmonary hypertension, which may be further aggravated by left ventricular underdevelopment.[3,4] Management of infants with CDH has included therapy directed toward the treatment of persistent pulmonary hypertension: neuromuscular blockade, sedation, alkalosis (respiratory and/or metabolic), and the use of alternative forms of ventilatory support including high-frequency oscillatory ventilation (HFOV). As of July 1995, over 2000 infants with CDH have been treated with extracorporeal membrane oxygenation (ECMO), 58% of whom survived.[5] In the most recent prospective evaluation of infants with CDH, the ECMO trial in the United Kingdom, all 17 control infants with CDH died, compared with 14 deaths among the 18 ECMO-allocated infants.[6] In addition to the high inherent mortality, CDH ranks among the most costly of correctable conditions, with an estimated cost per new case of $250 000, and an overall estimated yearly cost of $364 000 000 in the United States.[7]

The most common indication for ECMO in infants with CDH is persistent hypoxemia, thought to be secondary to persistent pulmonary hypertension. Regulation of vascular smooth muscle tone is significantly influenced by nitric oxide (NO), which is felt to be identical to the previously described endothelium-derived relaxing factor (EDRF)[8–14]. NO is generated enzymatically by nitric oxide synthase from the precursor L-arginine.[15] NO diffuses from the vascular endothelium into the vascular smooth muscle

This study is a collaboration of the NICHD Neonatal Research Network and the Canadian Inhaled Nitric Oxide Study Group (see Appendix).
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where it activates guanylate cyclase leading to the production of cyclic guanosine monophosphate.[16,17] The subsequent relaxation of vascular smooth muscle by cyclic guanosine monophosphate may involve the inhibition of activation-induced elevation in cytosolic calcium concentration.[18]

Inhaled nitric oxide (INO) is a selective pulmonary vasodilator in animal models[19–22] and in adults, improving oxygenation without producing a decrease in systemic vascular resistance.[23–25] Preliminary reports[26–28] demonstrated that INO improved oxygenation in infants with persistent pulmonary hypertension of the newborn (PPHN) and hypoxic respiratory failure with Roberts et al using 80 ppm, whereas Kinsella[27] used 20 ppm followed by 6 ppm. A subsequent study found that among responsive infants there did not appear to be significant differences in the responses observed using doses from 5 to 80 ppm.[29]

Preliminary experience with the use of INO in infants with CDH has suggested that the majority of infants with hypoxemic respiratory failure treated shortly after delivery did not show sustained beneficial responses, but some infants showed an improvement of oxygenation after a course of ECMO.[30–34]

In view of these observations, a prospective multicenter randomized controlled trial was conducted to evaluate the ability of INO to prevent death or the initiation of ECMO in term and near-term infants with hypoxic respiratory failure unresponsive to aggressive conventional therapy.[35] Infants with CDH and hypoxic respiratory failure were enrolled in a separate parallel study; the results of that trial are reported in this article.

MATERIALS AND METHODS

Hypotheses

The primary hypothesis of the main trial[35] and the CDH trial was that the administration of INO to infants ≥34 weeks and an oxygenation index (OI) of >25 would reduce the risk of death by day 120 or discharge home (which ever came first) or the initiation of ECMO from 50% in the control group to 30% in the INO group, a relative reduction of 40%. The secondary hypotheses for the main trial were that administration of INO would lead to: an increase in Pao_2, a decrease in OI and A-aDO_2 measured 30 minutes after initial administration of INO, a decrease in hospital days, no increase in days of assisted ventilation, incidence of air leak, bronchopulmonary dysplasia (BPD), or neurodevelopmental disability at 18 to 24 months. Infants with CDH were enrolled in a separate parallel study that enrolled patients concurrently with the main trial.

Patient Population

Any infant ≥34 weeks by best obstetric estimate who required assisted ventilation for hypoxemic respiratory failure secondary to CDH and had two OIs [(OI = (MAP × FIo_2 × 100)/Pao_2] ≥25 at least 15 minutes apart was eligible for participation in the trial. In addition, all infants were required to have an in-dwelling arterial line and parental permission before randomization. All centers attempted to obtain a cranial and cardiac ultrasound before entering the infant in the study. Each study center obtained institutional review board approval before enrolling infants.

Exclusion Criteria

Infants were ineligible if they were >14 days of age; had known congenital heart disease; were enrolled in conflicting clinical trials; or if a decision had been made not to provide full treatment.

Patient Management

The study protocol provided for maximal conventional treatment before randomization but it did not specify pre-enrollment management. Each participating center was required to develop a standard management strategy to be used for the duration of this trial. General management guidelines were agreed to by all centers. These included: maintenance of mean arterial blood pressure >45 mm Hg with volume infusions and/or the use of vasopressors; attempted induction of alkalosis with either hyperventilation, infusion of alkali, or both (target pH range of 7.45–7.60); and rescue treatment with a bovine surfactant (BLES, BLES Biochemicals, London, Ontario, or Survanta, Abbott Laboratories, Columbus, OH) before randomization. The mode of ventilation (conventional vs high frequency) could not be changed after randomization, except as part of weaning from assisted ventilation. The use of such therapies as sedation, analgesia, neuromuscular blockade, tolazoline, bronchodilators, and postnatal steroids was permitted. ECMO, either veno-venous or veno-arterial, was initiated when center-specific criteria were fulfilled; minimal ECMO criteria included the following:

1. OI >40 on two arterial blood gases (ABGs) separated by at least 30 minutes or OI >35 for 4 hours;
2. A-aDO_2 >630 for 4 continuous hours or A-aDO_2 >620 for 12 continuous hours; or
3. Acute deterioration/unresponsiveness to medical therapy (any 2 of 4):
   - Pao_2 <55 Torr for >2 hours
   - pH <7.15, or <7.40 if alkalosis attempted, for >2 hours
   - Mean arterial blood pressure <40 Torr for >2 hours
   - Severe barotrauma (4 of 7 criteria):
     1. pulmonary interstitial emphysema/pseudocyst,
     2. pneumothorax/pneumomediastinum,
     3. pneumoperitoneum,
     4. pneumopericardium,
     5. subcutaneous emphysema,
     6. persistent air leak >24 hours, or
     7. mean airway pressure >15 cm H_2O.

Randomization

Randomization was accomplished as soon as possible after meeting eligibility criteria and obtaining a second OI ≥25. Infants were stratified by center and randomized using a permuted block design developed and managed by the George Washington University Biostatistical Coordinating Center. This system used a dedicated telephone system that included a procedure for validation and recall verification.

Study Gas Administration and Monitoring

Infants were randomized to a control group or to an INO treatment group (INO group). Control infants received 100% oxygen. If study gas could not be started within 15 minutes of the second or qualifying OI, a third ABG was obtained before study gas initiation. The third ABG was then considered the baseline ABG with respect to evaluating the response to study gas, which was started regardless of the calculated OI. Primary grade nitric oxide was supplied as 800 ppm in balanced nitrogen (Canadian Liquid Air, Montreal, Quebec or Ohmeda Inc, Liberty Corner, NJ) and was certified to be ± 1% of the analyzed component (NO), and to contain <5 ppm nitrogen dioxide (NO_2). Single-stage stainless steel diffusion-free regulators were used, which were flushed to ensure that any air or other by-products such as NO_2 were removed. The source gas was connected at a regulated pressure of 50 psi using Teflon tubing to the input port of a suitable flow meter, and then injected at the desired flow rate into the inspiratory circuit of a neonatal ventilator (gas flow of approximately 12 L/min or more). Quality assurance procedures were developed to insure accurate calibration of the NO/NO_2 analyzers and to prevent contamination of the NO source gas.[36,37]

The resulting gas mixture was sampled between the injection site in the inspiratory circuit and the infant, and continuously analyzed for NO, NO_2 and total oxides of nitrogen using a chemiluminescence analyzer (Model 42H, Thermo Environmental Instruments Inc, Franklin, MA, or EcoPhysics, Durnten, Switzerland) or an electrochemical analyzer, (Pulmonox II, Tofield,

Alberta, Canada). Exhaled gas and exhaust from the analyzers were scavenged.

Infants were managed by the clinical team except during initiation or change of study gas concentration. Administration of study gas was masked by using designated, unmasked individuals (respiratory therapists, research nurses or physicians) in each collaborating center to obtain the randomization assignment, to set up the inhalational apparatus and the NO monitoring equipment, to adjust study gas concentrations, and to make mock adjustments to control infants. These individuals recorded the inspired oxygen, the study gas concentration, and the levels of NO and NO_2 every 2 hours and after changes in ventilator settings to ensure that the appropriate study gas concentration was being administered and that NO and NO_2 concentrations were not increased. The analyzer readings were covered at all times to ensure masking from the clinical team. In addition, the identity of the study gas tanks were masked. During administration of study gas, the inspiratory oxygen was determined using an online oxygen sensor in the inspiratory circuit before the site of study gas administration.

For this study, a positive response was defined as an increase in arterial Pao_2 above baseline 30 minutes after initial exposure to the study gas (full response >20 Torr; partial 10 to 20 Torr; no response <10 Torr). These values could be on preductal or postductal ABGs, but the comparison required sampling from the same site.

Infants were treated with the lowest study gas concentration to which they were responsive. Study gas was initiated at 20 ppm NO/control; it was continued in infants who achieved a full response 30 minutes after initiation of study gas. In infants who had less than a full response, study gas was stopped for 15 minutes if tolerated, another ABG was obtained, study gas was increased to the maximal concentration of 80 ppm NO/control, and a follow-up ABG obtained 30 minutes later. This methodology was to allow for a further assessment of the need for 80 ppm as initially reported by Roberts et al.[26] Infants who had a full response to the maximal concentration remained on this increased concentration; if the response was partial, infants were continued at the lowest study gas concentration to which they had a partial response. Study gas was discontinued if they did not respond at either concentration. Study gas was also discontinued in an infant who deteriorated before the end of the initial 30-minute study gas administration period (absolute decrease in oxygen saturation >10%), and the infant was classified as a nonresponder. Infants who did not respond to the initial administration of study gas could be retried up to three times at 6-hour intervals. Crossover was not allowed between treatment groups.

Study Gas Weaning

After the initial study gas dosing, which was specified by the protocol, study gas management was at the discretion of the centers, using a recommended protocol for weaning and escalation of study gas. The maximal total duration of study gas administration was 336 hours (14 days). Weaning of study gas was only attempted if the Pao_2 was more than the acceptable baseline established by each participating center (the minimal criteria being an oxygen saturation >92% and/or a Pao_2 >50 Torr).

Study Gas Escalation

If, during continuous study gas administration, a deterioration occurred resulting in two OIs >25 and at least 50% more than the baseline OI measured at the last weaning attempt, the study gas concentration was doubled to a maximum of 80 ppm NO/control until a full response was obtained. The gas was returned to the pre-escalation concentration in unresponsive infants or to the lowest study gas dose to which the infant had had a partial response.

Study Gas Reinitiation

Study gas could be reinitiated after a successful wean if the patient had an OI ≥15 on two consecutive ABGs at least 30 minutes apart and had a less-than-the-maximum cumulative study gas exposure. Study gas was reinitiated at the concentration at which study gas was discontinued.

Safety Monitoring

Blood methemoglobin concentrations were measured at 1, 3, 6, and 12 hours after initiation of study gas and subsequently every 12 hours until 24 hours after gas discontinuation. Inhaled NO_2 concentrations were monitored continuously. Methemoglobin levels of 5 to 10% were managed with an immediate decrease in study gas concentration by 50% until the level fell to <5%. Study gas was immediately discontinued for methemoglobin level >10%. If NO_2 concentrations exceeded 7 ppm, study gas was immediately discontinued; it was decreased by 50% for NO_2 of 5 to 7 ppm. Infants weaned off study gas for elevated methemoglobin or NO_2 levels were not considered successfully weaned.

Infants were monitored for signs of increased bleeding, (ie pulmonary hemorrhage, gastrointestinal bleeding, or oozing from venipuncture sites). Cranial ultrasonography was performed whenever possible before randomization and 24 hours after final discontinuation of study gas. All readings were by local ultrasonographers and classification was based on the Papile classification.[38]

Statistical Considerations

Based upon the Extracorporeal Life Support Organization (ELSO) registry, we estimated that the potential population for the CDH study would be about 20% of the potential population for the main trial, which was estimated to require 125 non-CDH patients in each arm of the study to demonstrate a 40% reduction in the occurrence of death or the initiation of ECMO from 50% to 30%. Therefore, we believed that it was unlikely that we would be able to adequately test the primary and secondary hypotheses with the number of infants who could be enrolled (about 50 over 2 years). Thus, this trial was conducted to determine whether a larger trial would be indicated on the basis of the results. Tests of significance are based on t tests for means, the Wilcoxon statistic for medians, and on χ^2 statistics for discrete variables. The primary analysis used the intent-to-treat paradigm.

The main and CDH pilot trials were monitored by an independent Data Safety and Monitoring Committee (DSMC). The DSMC planned two evaluations after approximately one- and two-thirds enrollment for the primary trial. It was agreed that the CDH arm would end when the primary trial was completed, unless a specific recommendation to continue enrollment was made by the DSMC.

RESULTS

The primary non-CDH study was terminated after an evaluation by the DSMC determined that INO significantly reduced the incidence of the primary outcome, death before discharge or 120 days or the initiation of ECMO in term and near-term infants with hypoxic respiratory failure. Recruitment ceased on May 2, 1996. The CDH parallel trial was terminated at the same time as the main trial, on the recommendation of the DSMC, because of a lack of observable benefit, and the very low likelihood of such an effect with continued enrollment.

Baseline

Fifty-three infants with CDH were enrolled in the trial; Table 1 presents the descriptive information for this population. No significant differences between the control and INO-treated groups were noted for any of these variables. Overall, 76% of infants for whom an echocardiograph was performed (51 of 53) had evidence of PPHN, defined as either tricuspid regurgitation and/or bidirectional or right to left shunting at either the duct or foramen ovale, with similar proportions for control and INO infants. No differences between control and INO groups were noted in therapies used before randomization (Table 2). In addition, a similar number of infants in the

TABLE 1. Neonatal Demographics of Infants With CDH and Hypoxic Respiratory Failure

	Control	Treatment Group (INO)
	(n = 28)	(n = 25)
Birth weight (g) (mean ± SD)	3093.7 (525.8)	3049.7 (542.0)
Gestational age (wks) (mean ± SD)	38.0 (2.2)	38.8 (2.0)
Female	9 (32.1)	11 (44.0)
Race		
Black	1 (3.6)	4 (16.0)
White	24 (85.7)	17 (68.0)
Hispanic	1 (3.6)	1 (4.0)
Other	2 (7.1)	3 (12.0)
Outborn	16 (57.1)	16 (64.0)
Age at admission (outborns)		
Under 12 h	13 (81.3)	13 (81.3)
12–24 h	2 (12.5)	2 (12.5)
>24 h	1 (6.3)	1 (6.3)

Data expressed as n (%) unless otherwise indicated.

control and INO groups had air leaks (29 vs 28%) and pulmonary hemorrhage (11 vs 4%) before randomization. Finally, there were no differences between the control and treated groups in age at randomization or initial arterial blood gas values, including $Paco_2$, Pao_2, pH, OI, or MAP (Table 3). The mean and median intervals between the time of randomization and the initiation of study gas (24.9 ± 35.5 minutes for the control group vs 51.8 ± 147.3 for the INO group, median interval 11.0 vs 12.5 minutes) were not significantly different.

Outcome

Twenty-three of 28 control infants (82%) compared with 24 of 25 (96%) INO-treated infants met the primary outcome of death and/or the initiation of ECMO, results that were not significantly different (13.9% difference, 95% confidence interval −31%, 3.2%, Table 4). Twelve of 28 (43%) of control infants compared with 12 of 25 (48%) of treated infants died (ns), with significantly fewer (15 of 28) control infants (54%) compared with 20 of 25 treated infants, (80%) receiving ECMO ($P = .043$, Table 4). The age of the initiation of ECMO and the time between randomization and initiation of ECMO were not significantly different between the groups. Fifteen infants were randomized in non-ECMO centers, of whom 13 died or required ECMO (86.7%). Seven infants were transferred for ECMO (4 controls, 3 INO), 5 of whom received ECMO, and all 7 infants survived and were discharged home, whereas all 8 nontransported infants died (5 control, 3 INO). Veno-venous ECMO was used in 6 control infants and 10 NO treated infants, and 1 child in each group required conversion to veno-arterial from veno-venous ECMO. There were fewer deaths among control infants who received ECMO (4/15, 26.7%) than for INO infants who received ECMO (8/20, 40% ns). The overall mortality was 46%, 35% for infants receiving ECMO, and 67% for the remaining infants. The most frequent causes of death were withdrawal of support (8 control and 4 INO infants) and unresponsive respiratory failure [4 control and 6 INO infants (ns)]. Five infants in this trial were randomized after surgical repair (4 control and 1 INO infant). Of these 5, 1 control infant survived without ECMO and 3 of 4 control infants required ECMO and died. The single INO infant survived after ECMO.

There were no significant differences for any of the secondary outcomes between the control and treated

TABLE 2. Therapies Before Randomization

	Control		Treatment Group (INO)	
	N		*N*	
Neuromuscular blockade				
≤6 h of randomization	28	26 (92.9)	25	22 (88.0)
>6 h before randomization	22	16 (72.7)	18	13 (72.2)
any time before randomization	28	26 (92.9)	25	22 (88.0)
Vasopressor support				
≤6 h of randomization	28	23 (82.1)	25	22 (88.0)
>6 h before randomization	22	15 (68.2)	18	12 (66.7)
any time before randomization	28	24 (85.7)	25	23 (92.0)
Surfactant				
≤6 h of randomization	28	18 (64.3)	25	20 (80.0)
>6 h before randomization	23	8 (34.8)	19	4 (21.1)
any time before randomization	27	22 (81.5)	25	21 (84.0)
HFOV				
≤6 h of randomization	28	17 (60.7)	25	17 (68.0)
>6 h before randomization	22	6 (27.3)	17	2 (11.8)
any time before randomization	28	17 (60.7)	25	17 (68.0)
Alkalosis				
≤6 h of randomization	28	16 (57.1)	25	17 (68.0)
>6 h before randomization	22	9 (40.9)	18	7 (38.9)
any time before randomization	28	19 (67.9)	25	18 (72.0)
Tolazoline				
≤6 h of randomization	28	2 (7.1)	25	3 (12.0)
>6 h before randomization	22	2 (9.1)	18	1 (5.6)
any time before randomization	27	3 (11.1)	25	3 (12.0)
Post-natal steroids				
≤6 h of randomization	28	1 (3.6)	25	1 (4.0)
>6 h before randomization	22	1 (4.5)	18	0 (0.0)
any time before randomization	27	2 (7.4)	25	1 (4.0)

Data expressed as n (%) unless otherwise indicated.

TABLE 3. Randomization Information

	Control	Treatment Group (INO)
	(n = 28)	(n = 25)
Age at randomization (h, mean ± SD)	33.8 (63.6)	17.8 (39.2)
Median age at randomization (h)	13.4	9.4
% Surgery reduction of CDH prior to randomization	4 (14.3)	1 (4.0)
Initial qualifying ABG (mean ± SD)		
OI	45.8 (16.3)	44.5 (14.5)
MAP	16.9 (4.7)	17.3 (4.1)
Fio_2	1.0 (0.0)	1.0 (0.0)
Pao_2	39.0 (10.3)	40.5 (8.1)
$AaDo_2$	603.6 (40.3)	616.7 (32.6)
% Preductal at randomization	1 (3.6)	0 (0.0)
Mode of ventilation at randomization		
Conventional	13 (46.4)	11 (44.0)
HFOV	15 (53.6)	14 (56.0)

Data expressed as n (%) unless otherwise indicated.

TABLE 4. Primary Outcome

	Control	Treatment Group (INO)
	(n = 28)	(n = 25)
Death ≤120 days ECMO	23 (82.1)	24 (96.0)
Died	12 (42.9)	12 (48.0)
Received ECMO	15 (53.6)*	20 (80.0)*
No. died with ECMO	4	8
No. died without ECMO	8	4
If received ECMO (± SD)		
Age initiated (days)	0.7 (0.9)	1.3 (1.9)
Hours after randomization	7.1 (6.5)	10.0 (10.5)

Data expressed as n (%) unless otherwise indicated.
* $P = .043$.

infants (Table 5). Measurements performed 30 minutes after initiation of study gas demonstrated no significant increase in Pao_2 or decreases in OI or A-aDO_2 (Table 5). Twelve of 25 INO-treated infants responded (8 partial, 4 full) to 20 ppm NO/control compared with 5 of 27 controls (all partial responses, $P = .024$). Of all INO-treated infants who had a partial or no response at 20 ppm NO/control, only 2 infants had a partial response at 80 ppm NO/control, and no infant had a full response at 80 ppm NO/control. All control infants with no or a partial response at 20 ppm NO/control had no response to 80 ppm NO/control. The median duration of study gas administered was 1 hour for controls compared with 5 hours for INO infants ($P = .003$). A retrial of study gas was administered to 1 infant from each study group. Only 1 infant received study gas (NO) during transport and that infant survived. There were 4 infants evaluated at the study centers during the trial who were eligible for the trial but were not enrolled. All met ECMO criteria and received ECMO. Three died and 1 survived.

Adverse Events

There were no differences postrandomization between the groups in the incidence of ICH (4 INO vs 4 control). One treated infant and 2 control infants had Grade IV ICH on posttreatment cranial ultrasound. There were no significant differences in the occurrence of brain infarction (1 control vs 3 INO) or periventricular leukomalacia between the groups (2 treated vs 1 control). There were no significant differences for the occurrence of pulmonary hemorrhage, generalized oozing from venipuncture sites, or gastrointestinal bleeding between the groups. No infant required discontinuation of study gas because of toxicity secondary to elevated methemoglobin or NO_2 concentrations.

DISCUSSION

In this trial, we were unable to demonstrate a beneficial effect for INO in infants with CDH and hypoxic respiratory failure unresponsive to aggressive conventional therapy. While there was no difference in the occurrence of the primary outcome, significantly more INO-treated infants received ECMO. The outcome for infants who received ECMO compares favorably with the most recent results from the ELSO Registry,[3] which is a compilation of results obtained over a period of >10 years. The indices of gas exchange were improved in some (56%) infants receiving INO, but this effect was transitory and consistent with the observations of Shah et al.[31] Only 4 treated infants (16%) had a 20 Torr or more increase in Pao_2 with INO treatment, whereas no control infant had such an increase ($P = .024$).

The initial OI of both control and treated infants was well over 40, 45.8 vs 44.5, and at the second ABG, the OIs had increased to 61.6 in the control and 47.6 in the treated infants; overall, 82% of controls and 96% of the treated infants received ECMO and/or died. While we had estimated that OIs ≥25 would predict that 50% of the infants would require ECMO and/or die, the infants were more significantly compromised than we anticipated at entry, and experienced a very high rate of death or initiation of ECMO (88.7%).

Our results are consistent with the previous observations by Karamanoukian et al[30] who found that early treatment of INO was not associated with significant improvements in oxygenation in infants with CDH. INO therapy post-ECMO benefited a number of infants studied by Karamoukian et al[30] and Frostell et al,[32] suggesting that with improvement in lung volumes and perhaps increased endogenous surfactant production, INO might exert a beneficial effect. Shah et al[31] noted problems with the

TABLE 5. Secondary Outcomes

	Control	Treatment Group (INO)
Change from baseline (mean ± SD)		
Pao_2 (Torr)	1.1 (7.6)	7.8 (19.8)
OI	4.0 (14.8)	−2.7 (23.4)
A-aDo_2 (Torr)	−2.1 (7.9)	−5.6 (42.8)
Hospital stay (days, mean ± SD)		
All infants	38.8 (38.1)	38.3 (32.0)
For survivors	60.7 (36.3)	53.8 (25.3)
For infants who died	9.6 (11.7)	22.8 (31.3)
BPD		
All	9 (33.3)	5 (20.0)
28-day survivors	9 (52.9)	5 (31.3)

Data expressed as n (%) unless otherwise indicated.

development of tachyphylaxis and increased plasma nitrates and nitrites.[31]

In the fetal lamb model of CDH, Karamanoukian et al[39] demonstrated that nitric oxide synthase (NOS) was present in the main pulmonary trunks of CDH lambs; however, the functional presence and activity of NO was not evaluated. North et al[40] studied the Nitrofen-induced model of CDH in rats and measured both endothelial NOS (eNOS) and neuronal NOS (nNOS) in the ipsilateral CDH and control lungs. They found a similar concentration of nNOS protein in CDH vs control lungs whereas eNOS protein was decreased in the animals with CDH (58 ± 6 vs 100 ± 6%). They reported a parallel decline in eNOS mRNA in the CDH vs control lung (22 ± 8 vs 100 ± 31% in control) and suggested that the diminished eNOS gene expression may contribute to PPHN associated with CDH. These results support a possible physiologic role for INO in infants with CDH.

Karamanoukian et al[41] have suggested that prophylactic surfactant therapy improved the response to INO in an animal model of CDH. In the current study, a majority of the infants received surfactant within 6 hours of randomization (64% of controls vs 80% of treated infants) and overall 82% and 84% of control and treated infants received surfactant before randomization. In the animal study of Karamanoukian et al,[41] however, surfactant, to be effective, was given before the initiation of mechanical ventilation (prophylactic treatment), whereas later treatment at 30 minutes (rescue treatment) had no effect.[42] The distribution of surfactant would be improved in the fluid-filled fetal lung compared with surfactant administered postnatally, especially in infants with significant lung disease requiring mechanical ventilation.

We encouraged full conventional management of these infants before the administration of INO which is an unproven therapy for such infants, and encouraged the use of surfactant, which most infants received, as well as currently accepted therapies for pulmonary hypertension. As can be seen from Table 2, the great majority of infants in the study were treated with volume support, neuromuscular blockade, sedation, the use of vasopressors, and alkalosis. Sixty-four percent of infants overall were also treated with HFOV and at randomization, more infants were receiving HFOV than conventional ventilation (55% vs 45%, ns) (Table 3). It may well be that the use of these therapies delayed the initiation of the study gas and that INO used earlier may have been associated with a greater improvement. This question will need to be evaluated in an appropriately designed prospective trial.

The current study appears to be the largest prospective randomized controlled trial designed to evaluate a therapy for infants with CDH. Others include the UK ECMO trial[4] and Lotze et al,[43] who compared the effects of surfactant vs placebo in 17 infants with CDH who were receiving ECMO. Lotze et al found no difference in time to extubation, time on oxygen or duration of total hospitalization between the surfactant and placebo-treated groups. Nio et al[44] performed a nonblinded, randomized prospective trial evaluating early (within 6 hours) and delayed (96 hours or more) surgical repair of CDH in 32 infants and reported no difference in overall survival (75% for early and 72% for delayed) or the requirement for ECMO (67% for early vs 89% for delayed) between their groups.

Bos et al[45] in a nonrandomized, combined retrospective and prospective evaluation of infants with CDH noted that documented pulmonary hypertension occurred in 46% of 52 infants with CDH. They found that tolazoline did not improve oxygenation, and was associated with a significant decrease in blood pressure whereas prostacyclin did appear to improve oxygenation.

Although our numbers overall remain small, it is of interest that there were more deaths without ECMO in the control infants and more deaths with ECMO in the NO treated (both nonsignificant) suggesting the possibility that INO allowed some infants to survive to be cannulated who later died. NO therapy did not appear to unduly delay ECMO: control infants were placed on ECMO at seven hours compared with 10 hours for NO treated infants (ns), and all 7 infants who were transported for consideration of EMCO survived.

The confidence intervals of our results suggest that there may be a 3% likelihood that INO would be beneficial in reducing the occurrence of death or need for ECMO for infants with CDH and OIs similar to those seen in the current trial, balanced by the 31% possibility of a worse outcome for such infants. In addition, our trial did have sufficient power to reject a 25% reduction in the primary outcome with NO therapy using the methodology suggested by Detsky and Sackett.[46] Therefore, our results imply that treatment with INO, as used in this protocol, is unlikely to be of significant benefit in term and near-term infants with CDH who present with hypoxic respiratory failure and OIs >40, and may increase the need for ECMO in such infants.

However, further trials in infants with CDH may be required to assess the value of both earlier and later use of INO. In addition, although INO may help stabilize some infants during transport and/or cannulation for ECMO, its use should not delay appropriate consideration for ECMO. Our results encourage further research on the use of other supportive modalities, such as liquid ventilation,[47] for critically ill infants with CDH unresponsive to conventional management.

APPENDIX: CANADIAN INHALED NITRIC OXIDE STUDY GROUP (CINOS)

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Inhaled Nitric Oxide and Hypoxic Respiratory Failure in Infants With Congenital Diaphragmatic Hernia

The Neonatal Inhaled Nitric Oxide Study Group (NINOS)

Pediatrics 1997;99;838
DOI: 10.1542/peds.99.6.838

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EXHIBIT C

EXHIBIT 5

UNITED STATES PATENT AND TRADEMARK OFFICE	
Application Serial Number	12/820,866
Confirmation Number	2913
Filing Date	22-JUN-2010
Title of Application	METHODS OF TREATING TERM AND NEAR-TERM NEONATES HAVING HYPOXIC RESPIRATORY FAILURE ASSOCIATED WITH CLINICAL OR ECHOCARDIOGRAPHIC EVIDENCE OF PULMONARY HYPERTENSION
First Named Inventor	JAMES S. BALDASSARRE
Assignee	IKARIA, INC.
Group Art Unit	1616
Examiner	ARNOLD, ERNST V.
Attorney Docket Number	I001-0002USC1

Mail Stop Amendment
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, Research and Development at INO Therapeutics LLC ("INO"). A copy of my *curriculum vitae* is attached as **Exhibit 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, Penn, Pitt, 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 INO, where – as noted above – I am presently Executive Vice President and Head of Research and Development.

7. INO markets pharmaceutical grade nitric oxide (NO) gas under the brand name INOmax®. INOmax® is administered to patients using INO's proprietary INOvent® and INOmax® DS devices.

8. INOmax® was approved for sale in the United States by the U.S. Food and Drug Administration ("FDA") in 1999 for the treatment of term and near-term (≥ 34 weeks gestational age) neonates with hypoxic respiratory failure ("HRF") associated with clinical or echocardiographic evidence of pulmonary hypertension, a condition also known as persistent pulmonary hypertension in the newborn ("PPHN"). From 2000 to the present, INO has been selling INOmax® throughout the United States, Canada and certain other overseas markets.

9. In addition to the approved indication, physicians employ INOmax® to treat or prevent pulmonary hypertension and improve blood oxygen 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, and improves pulmonary gas exchange.

10. The mechanism of action of INOmax® - the selective relaxation of pulmonary blood vessels - is particularly relevant to the transition of the newborn from the fetal to the neonatal environment. During *in utero* development, the fetal lungs are not filled with air. Accordingly, the fetus obtains oxygen from the mother across the placenta into the systemic circulation, whereas the circulation through the lungs is largely shut down because the pulmonary vessels are tightly constricted. Instead of the blood being pumped from the right side of the heart through the fetal lungs and then returning to the left side of the heart to be pumped to the rest of the body, as it is normally after birth, blood from the right side of the fetal heart bypasses the fetal lungs through a patent ductus arteriosis, a blood vessel connecting the outflow of the right heart directly to the systemic circulation.

11. In addition to the patent ductus arteriosis, the fetal heart contains a second anatomical distinction from the neonatal heart - the foramen ovale - as a means for fetal blood to circumvent the nonfunctional fetal lungs while the fetus obtains its oxygen from the placenta. The foramen ovale is a "hole" located in the wall that separates the right and left atria of the heart. The foramen ovale is usually covered by a flap of tissue known as the septum primum, which is located on the inner wall of the left atrium. The septum primum and the foramen ovale together act as a one-way valve that permits blood to be shunted from the right atrium, where blood pressure is usually high due to the high vascular resistance present in the non-functional fetal lungs, into the left atrium for distribution to the body via the left ventricle. As discussed below, nonclosure of a patent foramen ovale after birth, as well as other forms of congenital heart disease, are often associated with a large persistently patent ductus arteriosis.

12. After birth, the pressure in the pulmonary circulatory system drops, reducing the right atrial pressure below that of the left atrium. This shift in pressure causes the septum primum to close off the foramen ovale, and this flap of tissue eventually becomes incorporated into the intra-atrial wall. In certain instances, however, the foramen ovale may remain open or "patent" after birth. In one such case, elevation of pressure in the pulmonary circulatory system (i.e.: pulmonary hypertension due to various causes) can prevent the pressure shift that leads to the closure of the foramen ovale. This condition is known as patent foramen ovale, and the use

of inhaled nitric oxide to decrease pulmonary hypertension is known to be a successful treatment for right-to-left shunting through a patent foramen ovale.[1]

13. At birth, the ductus arteriosis closes and pulmonary vessels relax, thereby redirecting the outflow of the right heart to the now oxygenated lungs, with oxygenated blood then returning to the left side of the heart to be pumped to the rest of the body from the left ventricle. However, in some instances, neonates are born with severe congenital heart disease involving the left ventricle, wherein the left side of the heart lacks the ability to pump blood to the rest of the body. In these instances, a ductus arteriosis that remains open or "patent" is actually beneficial, and in fact is life-saving when combined with pulmonary hypertension, because the reverse pressure created by the pulmonary hypertension creates a right-to-left shunt through the patent ductus arteriosis, thereby permitting the right ventricle to pump oxygenated blood directly to the systemic circulation to maintain organ function; simply put, the patent ductus arteriosis permits the right ventricle to subsume the role of nonfunctional left ventricle in circulating blood to the body. In these circumstances, stealing blood circulation away from the ductus arteriosis would be potentially fatal, and significantly, pulmonary vasoconstriction is also absolutely essential for survival in order to divert sufficient blood from the right heart through the patent ductus arteriosis to the systemic circulation, thus bypassing the non-functional left side of the heart to maintain life. The terminology to describe this situation is "neonates dependent upon right-to-left shunting of blood" for survival.

14. Administration of inhaled nitric oxide (iNO) in the context of such right-to-left shunting would be catastrophic, because reducing or eliminating the pulmonary vasoconstriction would permit blood to be diverted to the lungs and away from the patent ductus arteriosis.[2] Accordingly, an absolute contraindication for the use of iNO in babies dependent upon right-to-

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1 *See* Fessler MB et al., *Right-to-left shunting through a patent foramen ovale in right ventricular infarction: improvement of hypoxemic and hemodynamics with inhaled nitric oxide*. J. Clin. Anesth. 15: 371-4, 1993, at 371.

2 *See, e.g.,* Atz AM, Wessel DL. *Inhaled nitric oxide in the neonate with cardiac disease.* Sem. Perinatol. 21:441-455, 1997, at 452.

left shunting of blood has been contained in the INOmax® prescribing information since the original approval of INOmax® by the FDA in December, 1999.[3]

15. Pulmonary engorgement also occurs in adults with serious left-sided heart disease due to coronary artery disease ("ischemic cardiomyopathy"), hypertensive heart disease ("hypertensive cardiomyopathy") or obstructive valvular disease or other conditions that similarly restrict the inflow of blood to the left side of the heart such that engorgement of the pulmonary blood vessels ensues. It is important to note that restriction of left-sided inflow is particularly prominent in the above cardiomyopathies, and is described as diastolic dysfunction.[4] 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.[5]

16. To summarize, in adults, left-sided ventricular dysfunction is generally ischemic or hypertensive in origin, and is associated with a stiff, non-compliant left ventricle that cannot

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3 *See,* Exhibit 2, section 4, Prescribing Information, INOMAX.

4 *See* "Diastolic Dysfunction" American Heart Association "Learn and Live" website visited April 13, 2011: "The heart contracts and relaxes with each heartbeat. The contraction part of this cycle is called **systole** (SIS'-to-le). The relaxation portion is called **diastole** (di-AS'-to-le). In some people with heart failure, the contraction function is normal but there's impaired relaxation of the heart. This affects the heart's lower, pumping chambers (the ventricles) specifically. If the relaxation part of the cycle is abnormal, it's called diastolic (di"as-TOL'-ik) dysfunction. Because the ventricle doesn't relax normally, the pressure in it increases and exceeds what's normal as blood for the next heartbeat. (It's harder for all of the blood to go into the ventricle.) This can cause increased pressure and fluid in the blood vessels of the lungs. (This is called pulmonary congestion.) It can also cause increased pressure and fluid in the blood vessels coming back to the heart. (This is called systemic congestion.) People with certain types of cardiomyopathy (kar"-de-o-my-OP'-ah-the) may also have diastolic dysfunction."

5 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].

fill properly ("diastolic dysfunction"). In contrast, in children, left-sided ventricular dysfunction is generally not of 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, adult left ventricular diastolic dysfunction, but not childhood left ventricular systolic dysfunction, would lead to pulmonary vascular engorgement, requiring caution in the use of iNO.

17. Since the approval of iNO in December 1999, INO has from time-to-time sponsored, supported or otherwise facilitated - under its own FDA Investigational New Drug (IND) application or IND applications filed by other investigators - clinical research exploring the efficacy and safety of iNO in clinical contexts outside the approved indication for PPHN. The results of these investigations are submitted to the FDA and are often published in the medical literature. In May 2004, following detailed consultations with an expert steering committee composed of leading world authorities in pediatric heart and lung disease,[6] INO initiated a multinational randomized controlled 150-patient 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 Vasodilator Testing" ("INOT22"). Prior to its initiation, the INOT22 study was reviewed and approved by the Institutional Review Board (IRB) and/or Independent Ethics Committee (IEC) at each of the 18 participating study institutions, and by two independent National Health Authorities (the U.S. FDA and the European Medicines Agency (EMEA)). At no time did any of the members of these boards, committees or agencies counsel against giving inhaled nitric oxide to the proposed patient population because of the risk of severe adverse events in pediatric patients (i.e., children) with left ventricular dysfunction.

18. INOT22 was designed and purposed to compare the diagnostic utility of short-term (10 minute) inhalation of iNO alone, iNO plus oxygen ("O_2") or O_2 alone to children between the ages of 4 weeks and eighteen years with either idiopathic pulmonary arterial

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6 The steering committee included Dr. David Wessel of the Department of Cardiology, Children's Hospital and the Department of Pediatrics, Harvard Medical School.

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. The rationale for INOT22 were: (1) that in patients with right ventricular failure and lung disorders, the prognosis and course of treatment are determined by acute pulmonary vasodilatation testing (APVT); (2) a reduction in the mean pulmonary artery pressure and pulmonary vascular resistance with acute vasodilator treatment may be used to predict therapeutic efficacy of long-term vasodilator medication; and (3) APVT 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. Accordingly, the primary objective of INOT22 was to compare the number of patients who exhibited reversible pulmonary hypertension (vasoreactivity) in response to iNO or iNO plus and oxygen as compared to 100% oxygen alone.

19. Under the direction of the expert steering committee, inclusion and exclusion criteria were established that were intended to ensure the safe use of iNO during the conduct of the study. For example, patients dependent on right-to-left shunting and thereby contraindicated for iNO treatment were not included. Patients also were excluded if they had focal pulmonary infiltrates on chest radiograph, a diagnosis of severe obstructive or restrictive pulmonary disease that significantly contributed to the patient's pulmonary hypertension, had received treatment with iNO within 30 days prior to study initiation or were on other investigational medications, nitroglycerin, sodium nitroprusside, sildenafil, other PDE-5 inhibitors, or prostacyclin, or were pregnant.

20. However, since the inclusion criteria included congenital heart disease or cardiomyopathy, many of the patients had, by design, significant childhood heart disease. This was not considered to pose a significant risk by the experts on the steering committee (1) based on the exclusion of right-to-left shunt-dependent patients, (2) based on prior extensive safe experience with iNO in pediatric patients with congenital heart disease or cardiomyopathy by the

investigators and published in the medical literature,[7] and (3) the very different nature of non-ischemic non-hypertensive childhood heart disease from the ischemic or hypertensive adult form marked by diastolic dysfunction.

21. Surprisingly and unexpectedly, severe adverse events including pulmonary edema and death were noted during the early phase of the study, and the study was stopped. Analysis of the cases revealed that the patients suffering severe adverse events had severe left ventricular dysfunction, largely due to viral cardiomyopathy, and exhibited during their right-sided cardiac catheterizations an increased pulmonary capillary wedge pressure ("PCWP") of greater than 20 mm Hg, indicative of elevated pressures in the upper chamber of the left side of the heart (the left atrium).

22. To determine if there was a correlation between the severe adverse events and the left ventricular dysfunction of the patients that had suffered them, a protocol amendment was submitted to FDA to exclude – on an ongoing basis - patients with severe left ventricular dysfunction with a PCWP greater than 20 mm Hg from further enrollment in the study. The study was then completed. On analyzing the data from the study, the inventors concluded that a correlation did, in fact, exist between the severe adverse events that had occurred during the study and the left ventricular dysfunction of the patients that had suffered them. Accordingly, INO subsequently requested that the FDA add an additional warning to the product labeling for INOmax concerning use of the drug within patients with left ventricular dysfunction. The FDA agreed and included an additional warning in section 5.4 and the Warnings and Precautions section of the INOmax prescribing information (in the US and worldwide).[8]

23. Competent practitioners would understand that the warnings included in section 5.4 and the Warnings and Precautions section of the INOmax prescribing information are intended as a separate warning generally applicable to all patients with left ventricular dysfunction and not limited to those patients having left ventricular dysfunction that also rely on

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7 *See* Atz AM et al. *Combined effects of nitric oxide and oxygen during acute pulmonary vasodilator testing.* J. Amer. Coll. Cardio. 33:813-819, 1999, at 814, 818.

8 *See* **EXHIBIT 2.**

right to left shunting of blood. This second category of patients is the subject of a separate section of the US Package Insert which expressly provides that INOmax is contraindicated for patients with this condition. The fact that administration of INOmax would be harmful to patients dependent on right to left shunting of blood has been well known for many years as demonstrated by several of the references that are of record in the present case including [e.g., Atz AM, Wessel DL. *Inhaled nitric oxide in the neonate with cardiac disease.* Sem. Perinatol. 21:441-455, 1997].

24. Furthermore, no competent practitioner would understand the separate warnings in section 5.4 and the Warnings and Precautions section of the INOmax prescribing information, or the disclosure in the present application of the potential for severe adverse events in patients with left ventricular dysfunction as referring to patients dependent on right to left shunting of blood, since it has long been known that the use of INOmax is contraindicated in such patients. Rather, the competent practitioner would understand the additional warnings added at section 5.4 and within the Warnings and Precautions section of the INOmax prescribing information, and the disclosure in the present application of the potential for severe adverse events in patients with left ventricular dysfunction, as a distinct and separate warning and disclosure that administration of INOmax to patients with left ventricular dysfunction generally (even those not dependent on right to left shunting of blood) may result in serious adverse events.

25. 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 the '359 patent.

26.

Dated April 29, 2011

Douglas A. Greene

Douglas A. Greene, M.D.

EXHIBIT D

Exhibit B

UNITED STATES PATENT AND TRADEMARK OFFICE	
Application Serial Number	12/820,866
Confirmation Number	2913
Filing Date	22-JUN-2010
Title of Application	METHODS OF TREATING TERM AND NEAR-TERM NEONATES HAVING HYPOXIC RESPIRATORY FAILURE ASSOCIATED WITH CLINICAL OR ECHOCARDIOGRAPHIC EVIDENCE OF PULMONARY HYPERTENSION
First Named Inventor	JAMES S. BALDASSARRE
Assignee	IKARIA, INC.
Group Art Unit	1616
Examiner	ARNOLD, ERNST V.
Attorney Docket Number	I001-0002USC1

Mail Stop Amendment
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 **Exhibit 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, Penn, Pitt, 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 INO, where – as noted above – I am presently Executive Vice President and Head of Research and Development.

7. I have been shown a Non-Final Office Action issued by the United States Patent and Trademark Office (USPTO) on June 8, 2011 in a pending patent application having US serial number 12/820,866. This Non-Final Office Action rejected the pending claims of 12/820,866 as "obvious" based on clinical interpretations presented by the USPTO regarding the teaching and disclosure of Atz & Wessel. (Seminars in Perinatology 1997, 21(5), 441-455), Kinsella et al. (Lancet 1999, 354 1061-1065) and Loh et al. (Circulation 1994, 90, 2780-2785). Below is my professional opinion and interpretation of the arguments and clinical interpretations presented by the USPTO within the Non-Final Office Action of June 8, 2011, for 12/820,866 (the "Office Action).

8. On page 7 of the Office Action, the Examiner states:

> *"Atz et al. teach that: 'Caution should be exercised when administering NO to patients with severe left ventricular dysfunction and pulmonary hypertension.' (page 452, left column)."*

A more complete excerpt from Atz & Wessel, p. 452, left column is as follows:

> "Caution should be exercised when administering NO to patients with severe left ventricular dysfunction and pulmonary hypertension. In **adults with ischemic cardiomyopathy,** sudden pulmonary vasodilation may occasionally

> unload the right ventricle sufficiently to increase pulmonary blood flow and harmfully augment preload in a compromised left ventricle. The attendant increase in left atrial pressure may produce pulmonary edema. ... A different but related phenomenon may be operative in the newborn ...." (emphasis added)

Thus, although Atz & Wessel warns that "[c]aution should be exercised when administering nitric oxide (NO) to patients with severe left ventricular dysfunction and pulmonary hypertension[,]" this caution is specifically limited to two populations of patients. In the first population, the statement in Atz & Wessel p. 452, left column, is directed to adult patients with ischemic cardiomyopathy who also exhibit severe left ventricular dysfunction and pulmonary hypertension. This patient population is clearly different from the neonatal population that is the object of the teaching of the present claims.

9. Further in the same paragraph, Atz & Wessel specifically refers to a second patient population, which is also distinct from that of the present patent application, to whom inhaled NO should not be administered, namely, neonates depending on right-to-left shunting of blood:

> "A different but related phenomenon may be operative in the newborn with severe left ventricular dysfunction and pulmonary hypertension. In these patients, the **systemic circulation may depend in part on the ability of the right ventricle to sustain cardiac output through a right-to-left shunt across the patent ductus arteriosus.** Selective pulmonary vasodilation may redirect the right ventricular output to the lungs and away from the systemic circulation." (emphasis added)

For this second patient population, Atz & Wessel state that these patients exhibit a "different but related phenomenon" from that observed in adults with ischemic cardiomyopathy. This second population of patients consists of newborn patients with congenital heart disease and left ventricular dysfunction who are **dependent on a right-to-left shunt through a ductus arteriosus** in order to maintain peripheral circulation necessary to survive. In these patients, a patent ductus provides the only alternate pathway for blood being pumped by the right ventricle to **bypass the dysfunctional left ventricle** and thereby substitute for the dysfunctional left ventricle in providing life-sustaining blood flow to the peripheral circulation. Blood emerging

from the right ventricle has only two possible pathways, either through the pulmonary circulation and then back to the dysfunctional left ventricle, or to pass through the patent ductus arteriosus in a right-to-left shunt to reach the systemic circulation. Inhaled NO dilates the pulmonary circulation, and therefore would divert blood to the lungs at the expense of the patent ductus arteriosus and systemic circulation, causing systemic vascular collapse and death. Again, this second patient population described by Atz & Wessel is also completely different from the patient population addressed in the present claims, which is term or near term neonates with left ventricular dysfunction who are **NOT dependent upon right-to-left shunting.**

10. The risk of circulatory collapse in the subset of newborns with congenital heart disease and severe left ventricular dysfunction **who are dependent upon a right-to-left shunt** through a patent ductus arteriosus was well known in this field long before the Atz & Wessel publication, as evidenced by the contraindication stated in the US Food and Drug Administration (FDA) prescribing information for INOMAX® (nitric oxide) for inhalation from the time of its initial approval by the FDA in 1999: **"CONTRAINDICATIONS:** Neonates known to be dependent on right-to-left shunting of blood".

11. As a result of the INOT22 study, it was recognized that a second population of neonates existed, distinct from the population described in Atz & Wessel, that had an increased risk of adverse events when inhaled NO was administered, namely: pediatric patients with left ventricular dysfunction **who are not dependent upon right-to-left shunting of blood.** In view of this newly identified risk, the FDA imposed the addition of a distinct and separate precaution to the prescribing information for INOMAX specifically cautioning about an additional risk of pulmonary edema for patients with left ventricular dysfunction (see paragraph 15). It is important to note that patients covered in the pre-existing contraindication (specifically neonates known to be dependent on right-to-left shunting of blood) were completely excluded from INOT22 by virtue of the labeled contraindication. The newly discovered risk of adverse events in neonates and children with left ventricular dysfunction **who are not dependent on right-to-left shunting** was not addressed, suggested or otherwise inferred from the teachings of Atz & Wessel, because when Atz and Wessel recommend that inhaled NO should be used with caution

"if at all", that warning relates to neonates **who are dependent upon right-to-left shunting of blood** – a completely different population of patients than the population that is addressed in the present claims.

12. On page 7 of the Office Action, the Examiner further states:

> *"Since pulmonary hypertension is instantly claimed, then the subject intrinsically has hypoxic respiratory failure."*

This statement is not medically accurate. Pulmonary hypertension occurs in many conditions other than hypoxic respiratory failure, such as congenital heart disease, maternal use of serotonin reuptake inhibitors, idiopathic pulmonary hypertension, etc.

13. On page 7 and 8 of the Office Action, the Examiner states:

> *"Atz et al. continues with: 'Therefore, in newborns with severe left ventricular dysfunction, predominantly left to right shunting at the foramen ovale and **exclusively right to left shunting at the ductus arteriosus**, NO should be used with extreme caution, if at all. We and others have reported adverse outcomes in this circumstance.' (p. 452, left column) (emphasis differing from original)."*

This statement merely reiterates the "caution" delivered by Atz & Wessel for the second population of patients identified in that publication, namely neonates **dependent upon a right-to-left shunt** at the ductus arteriosus. In this statement, Atz & Wessel simply teach that patients with severe left ventricular dysfunction dependent upon an exclusively right-to-left shunt at the ductus arteriosus often have coexistent predominantly left-to-right shunt at the foramen ovale. This additional left-to-right shunt at the foramen ovale, upstream from the dysfunctional left ventricle, permits blood to bypass the dysfunctional left ventricle and enter the right side of the heart, thereby enhancing the ability of the right ventricle to pump sufficient blood through the ductus arteriosus to maintain the systemic circulation. The population of patients dependent upon right-to-left shunting of blood (with or without shunting at the foramen ovale) was already excluded by the pre-existing FDA-mandated contraindication for inhaled NO, and is distinct from the patient population addressed in the present claims.

14. On page 8 of the Office Action, the Examiner states:

> *"Atz et al. thus identify conditions in the patients which is screening of the patient. Thus, Atz et al. fairly teaches excluding patients which include neonates with left ventricular dysfunction from inhaled NO treatment because the Examiner interprets "if at all" to mean no treatment and hence exclusion from treatment. The left ventricular dysfunction is intrinsically pre-existing."*

This statement misinterprets the teaching of Atz & Wessel. Specifically, "if at all" refers to the second patient population, wherein no treatment is allowed in the population of newborn "patients dependent upon right-to-left shunting of blood" who are at risk for circulatory collapse. Because these patients were already contraindicated in the drug labeling for inhaled NO prior to INOT22 (see paragraph 10 above), they were excluded from INOT22 and more importantly, are distinct from the patients identified in the new inhaled NO safety warnings mandated by the FDA in view of the risk that was newly identified as a result of the INOT22 study.

15. On February 25, 2009, INO Therapeutics LLC (owner of NDA 20845) submitted a label supplement to the FDA seeking to amend the prescribing information (i.e., the "label") for INOMAX® (nitric oxide) for inhalation, to include a new warning statement based on the unexpected outcome of the INOT22 study On August 28, 2009, the FDA approved the INOMAX® label supplement to include 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).*

Thereafter, similar warnings were added to the INOMAX label by Health Authorities in Japan, Europe, Canada and Australia. The FDA (and it's counterparts in foreign nations) would

not add new warnings and precautions to the label of an approved drug that merely restate a known contraindication already existing on the approved drug label. Indeed, the new FDA-approved warnings for the use of nitric oxide are clinically distinct from the existing, original INOMAX contraindication disclosed by Atz & Wessel, with respect to neonates dependent on right-to-left shunt.

16. On page 8 and 9 of the Office Action, the Examiner states:

> *"Kinsella et al. teach excluding patients (premature neonates) from inhaled nitric oxide treatment if they have fatal congenital anomalies or congenital heart disease (Abstract and p. 1062, Methods). Since left ventricular dysfunction is a congenital heart disease, as acknowledged by Applicant, (see specification [0028]), and it would be pre-existing, then the methods of Kinsella et al. intrinsically exclude this patient population from the method. ... The intended patient population is intrinsically at risk of one or more adverse events. Patients are intrinsically identified for nitric oxide inhalation treatment, diagnosed for congenital heart disease which intrinsically includes left ventricular dysfunction, and if the patient meets the criteria then treatment with NO is performed thereby reducing the risk of adverse events associated with the treatment."*

Based on these statements, it is clear that the Examiner fails to understand several critical aspects of the study of Kinsella et al.

17. First and foremost, the patients included in the Kinsella et al. trial were premature neonates who have severe respiratory failure due to immature lungs and surfactant deficiency, rather than term and near-term neonates suffering from pulmonary hypertension. In addition, none of the premature neonates enrolled in Kinsella et al. suffered from pulmonary hypertension. Thus, the patients included in Kinsella et al. were clinically differentiated, by age, etiology and pathophysiology, from the term and near-term neonates addressed in the present claims.

18. Secondly, exclusion of patients from a particular study may occur for a variety of reasons. For example, clinical trial inclusion and exclusion criteria are often chosen to define or restrict the study population in order to maximize homogeneity, thereby minimizing the presence of potentially confounding factors. This exclusion greatly facilitates the interpretation of the

study results, and increases the soundness of the conclusions reached in the study. Accordingly, patients with background disease sufficiently severe to overwhelm or confound an expected treatment effect are systematically identified and excluded quite independently from considerations of anticipated safety or efficacy of the test article in this particular patient group.

19. For example, patients with malignancy are often excluded from non-oncologic clinical trials, not because the test agents are unsafe, pose any specific risk in this population, or will not work, but rather because the clinical results will be confounded by the wholly unrelated effects of the underlying malignancy, thereby reducing the power of the clinical trial to answer a specific hypothesis regarding the test treatment. As a specific example, exclusion of patients with malignancy or advanced heart failure from cholesterol lowering trials does not imply that statins are unsafe or ineffective in these patients, but rather that their inclusion would confound the potential effects of statins on overall mortality or cardiovascular events.

20. In the specific case of Kinsella et al., it is clear that one of ordinary skill in the art would understand that the patients having fatal congenital anomalities or congenital heart disease were excluded not because of a suspected safety risk of treating these patients with inhaled NO (e.g., a risk of pulmonary edema), but rather solely because the inclusion of such patients would have made it much more difficult – if not impossible - for Kinsella et al. to interpret the target outcomes of the study (i.e., would have "confounded" the results).

21. On page 9 of the Office Action, the Examiner states:

> *Loh et al. teach that inhaled nitric oxide in patients with left ventricular dysfunction may have adverse effects in patients with LV failure (Title and Abstract). Loh et al. clearly teaches that patients with pulmonary artery wedge pressure, which is synonymous with the instantly claimed pulmonary capillary wedge pressure, of greater than or equal to 18mm Hg had a greater effect of inhaled NO due to the greater degree of reactive pulmonary hypertension present in such patients (p. 2784, left column). Loh et al. state: "Since the degree of reactive pulmonary hypertension is generally related to the severity of hemodynamic compromise in patients with LV failure, it might be*

anticipated that patients with more severe heart failure will have a more marked hemodynamic response to inhaled NO." Loh et al. examined this prediction further and verified it (p. 2784, left column).

The Examiner apparently neglects to consider that the acute hemodynamic effect of inhaled NO was studied by Loh et al. only in **adult** patients with New York Heart Association Class III or IV congestive failure due to coronary artery disease or dilated cardiomyopathy, not in term or near-term neonates who were not dependent upon right-to-left shunting. Thus, their observations do not teach, or even suggest, the risk of inhaled NO in neonates or children with pulmonary hypertension and left ventricular dysfunction who are not dependent on right-to-left shunting of blood, the population that is addressed in the present claims.

22. The underlying etiologies and hemodynamic characteristics of both the primary heart disease and the increased pulmonary vascular resistance are drastically different from adults, as compared to non-adults, such that one cannot readily assume or anticipate clinical results within adults to translate into 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. Class III or class IV congestive heart failure in adults (in contrast to congenital heart disease in neonates or children) 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.

23. On page 10 of the Office Action, the Examiner states:

> *"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 Atz et al. and identify patients with a second condition/risk factor and administer iNO to patients that do not have the first or second condition/risk factors of instant claims 20-27 and inform the medical provider that patients with a pulmonary capillary wedge pressure greater than 20 mm Hg that may increase pulmonary edema, as suggested by Loh et al., and Kinsella et al., and produce the instant invention."*

24. Atz & Wessel do not recommend exercising "caution" when treating term or near-term neonates who are not dependent upon right-to-left shunting, but rather refer to two **other** patient populations, namely (i) neonatal patients whose systemic circulation is dependent upon right-to-left shunting of blood and who therefore might suffer from systemic circulatory collapse if given inhaled NO (a well-known contraindication for inhaled NO) and (ii) adult patients with New York Heart Association Class III-IV heart failure due to ischemic or dilated cardiomyopathy and increased neuro-humorally-mediated pulmonary vascular resistance might be hemodynamically at risk for pulmonary edema if given inhaled NO (the same population discussed by Loh et al.).

25. On page 10 of the Office Action, the Examiner states:

> *"One of ordinary skill in the art would have been motivated to do this because: 1) it is common sense that if the neonate is healthy then iNO therapy can be performed safely; 2) if the neonate is not healthy and has left ventricular dysfunction (LVD), then Atz et al. clearly teach using extreme caution or not using NO at all in the treatment of patients with LVD which would also render obvious all conditions/risk factors associated with LVD; and 3) the art of Kinsella et al. establishes excluding certain patients (premature neonates) from inhaled nitric oxide treatment if they have fatal congenital anomalies or congenital heart disease."*

The conclusion presented by the Examiner is not clinically accurate, nor does it accurately reflect the expectations or motivations of a clinician of ordinary skill in the art at the time of the invention. Their expectation would have been quite the opposite. It is by no means "*1) ... common sense that if the neonate is healthy then iNO therapy can be performed safely; 2) if the neonate is not healthy and has left ventricular dysfunction (LVD), then Atz et al. clearly teach using extreme caution or not using NO at all in the treatment of patients with LVD.*" Firstly, inhaled NO would have no utility in healthy neonates, and is safely used in very severely ill neonates on a routine basis. Secondly, Atz & Wessel teach "using extreme caution or not using NO at all" only in neonates dependent upon right-to-left shunting of blood in order to avoid systemic circulatory collapse, and makes no statement regarding neonates with left ventricular dysfunction **who are not dependent upon right-to-left shunting.** Kinsella et al. do not teach about the safe or unsafe use of inhaled NO in neonates or children, let alone term or near-term neonates not dependent upon right-to-left shunting, but merely noted that they had excluded premature babies with fatal malformations or congenital heart disease from a clinical trial of inhaled NO in premature babies suffering from the respiratory distress of prematurity. Loh et al. teach about the effect of inhaled NO on hemodynamic measurements in adults with advanced heart failure and secondary neuro-humorally-mediated increased pulmonary vascular resistance, and speculate that these adults may be at increased risk for pulmonary edema, but do not teach anything about the use of inhaled NO in term or near-term neonates not dependent upon right-to-left shunting.

26. On page 11 of the Office Action, the Examiner states:

> "*Furthermore, it is already known through the teachings of Loh et al. that a pulmonary capillary wedge pressure (PCWP) of greater than 18 mg Hg serves as a guidepost for alerting the artisan to adverse events from inhaled NO. Thus, it is not inventive to exclude patients with a PCWP of greater than 20 mm Hg when the art already suggests the risk of trouble of treating patients with a PCWP of 18 mm Hg because inhaled NO increases the wedge pressure as taught by Loh et al. (see entire document). In summary, it remains the position of the Examiner, which is in alignment with the written opinion of the international search authority, that it is simply not inventive to 'inform' a medical provider that a neonate with LVD is at risk of adverse/serious adverse*

> *events from iNO therapy when the art already has established that fact and the ordinary artisan is alerted to this fact. If the patient has LVD then they are at risk of adverse and/or serious adverse events from iNO therapy and it is not inventive to further identify other secondary conditions/risk factors associated with LVD and provide further warnings for secondary conditions/risk factors that are separate and independent from the first condition/risk factor but nevertheless associated with LVD to the medical provider. Screening for conditions that predispose the patient to adverse/serious adverse effects from medical treatment is obvious given the teachings above.*" (emphasis in original)

It is inaccurate to represent Loh et al as "*serving as a guidepost for alerting the artisan to adverse events from inhaled NO,*" as Loh et al. reported no adverse events during administration of inhaled NO for 10 minutes to 19 stable patients with advanced heart failure. Rather, Loh et al. speculated that a finding of an elevation in PCWP in a subgroup of such patients could pose an increased risk of pulmonary edema in adults with congestive heart failure due to ischemic or dilated cardiomyopathy. As discussed above, extrapolation of that theoretical risk to neonates and children with different forms of heart disease, different cardiovascular hemodynamics, and different pulmonary vasculature physiology, pathophysiology and pathology was not obvious , as evidenced by the fact that the members of the INOT22 Screening Committee (including Dr. Wessel) who designed the INOT22 study protocol, the approximately 18 Institutional Review Boards and/or Independent Ethics Committee, and 5 National Health Authorities (FDA and national Health Authority for United Kingdom, France, Netherlands and Spain) who reviewed and approved the INOT22 study protocol prior to its initiation, all failed to predict that any untoward effects would be caused by the administration of inhaled NO within a pediatric patient population having left ventricular dysfunction who are not dependent on right-to-left shunting of blood.. Only after being informed of the present invention did the FDA mandate a change to the drug labeling for inhaled NO to include a new warning (separate and distinct from the pre-existing contraindication pertaining to neonates dependent on right-to-left shunting of blood) concerning the use of inhaled NO in patients with pre-existing left ventricular dysfunction.

27. On page 12 of the Office Action the Examiner states:

Respectfully, the instantly claimed method steps are in the realm of common sense and not in the realm of invention because it is already known in the art that patients with pre-existing LVD are at risk of adverse effects from iNO. It is obvious to the ordinary artisan that if the neonate has LVD with or without any number of conditions/risk factors, then in order to avoid the risk of adverse or serious adverse events associated with iNO, to then exclude the neonate from iNO therapy. In other words, given the art as a whole, determination of further conditions/risk factors that would exclude the neonate from iNO therapy is obvious given the teachings in the art as discussed above which direct the artisan to screen neonates about to undergo treatment with NO by inhalation and to exclude those with LVD from such treatment. 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."

The arguments by which this conclusion is supported are both medically and scientifically unsound. To summarize, the teaching of Atz & Wessel is inaccurately portrayed by the Examiner due to his confusion of the known risk of systemic vascular collapse if inhaled NO is administered to neonates dependent upon right-to-left shunting of blood, and the opposite case of adults where inhaled NO may be less effective than in children. The Examiner misconstrues Kinsella et al.'s clinical trial inclusion/exclusion criteria as a teaching of risk associated with inhaled NO administration, rather than as a routine practical measure in the design of clinical trials to minimize confounding factors and heterogeneity in the study population. Lastly, the Examiner grossly over-interprets the hemodynamic findings of Loh et al. in adults with ischemic or dilated cardiomyopathy and congestive heart failure (a disease process differing in etiology, physiology, pathophysiology and pathology from childhood congenital heart disease) as "*a guidepost to the artisan*" regarding the use of inhaled NO in children and neonates with pulmonary hypertension and left ventricular dysfunction, but not dependent on right-to-left shunting of blood. These inaccurate and erroneous interpretations of all three supporting publications cited by the Examiner lead the Examiner to draw incorrect conclusions regarding what is or is not taught or suggested by the prior art.

28. On June 28, 2011, I met with Dr. David L. Wessel, the chair of the INOT22 Steering Committee and the senior author of *Atz & Wessel (Seminars in Perinatology 1997, 21(5), pp 441-455*. During our discussion, I informed Dr. Wessel of the 12/820,866 and 12/820,980 patent applications, and the fact that in both pending patent applications, the Examiner was citing Atz & Wessel to allege that it would have been obvious to predict the adverse events and outcomes of the INOT22 study that lead to the inventions claimed in 12/820,866 and 12/820,980.

29. Dr. Wessel disagreed with the Examiner's allegation and found it ironic that his own publication would be cited to suggest the obviousness of the unexpected outcomes of the INOT22 study, when Dr. Wessel himself, the senior author of Atz & Wessel, failed to predict that neonatal and child patients with left ventricular dysfunction who are not dependent on right-to-left shunting of blood would be at increased risk of adverse events when administered inhaled NO. A copy of a June 29, 2011 letter from Dr. Wessel to me stating this opinion is attached hereto as Exhibit 2.

30. 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 the '359 patent.

Dated: 7/7/11

Douglas A. Greene, M.D.

EXHIBIT E

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 $PCWP_2$ 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

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EXHIBIT F

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
ARNOLD, ERNST V	
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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 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

EXHIBIT G

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

~~followingin~~ 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

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EXHIBIT H

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	: James S. Baldassarre et al.	Art Unit	: 1613
Serial No.	: 12/821,020	Examiner	: Ernst V. Arnold
Filed	: June 22, 2010	Conf. No.	: 3179
Title	: Methods of Reducing the Risk of Occurrence of Pulmonary Edema in Children in Need of Treatment with Inhaled Nitric Oxide		

SUPPLEMENTAL AMENDMENT

This application has been granted special status under the prioritized examination (Track 1) program. An Office action was mailed January 31, 2012, setting a three-month deadline for response of April 30, 2012. The Examiner informed applicants' representative by telephone on April 23, 2012, that the Office action would be withdrawn and replaced with a new Office action. Although no written paper to that effect has been received by applicants' representative as of the date this Supplemental Amendment is being filed, the transaction history for this application on PAIR does have two entries dated April 24, 2012: "Mail Notice of Withdrawn Action" and "Withdrawing/Vacating Office Action Letter." Applicants thus assume that there is no longer a pending deadline for response, and there will be no deadline for response until the new Office action is mailed and thereby resets a new deadline.

Applicants ask that the below amendment to the claims be entered and the new Office action be based on the amended claims.

Amendments to the Claims

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

Listing of Claims:

1-30. (Canceled)

31. (Currently amended) A method of reducing the risk of occurrence of pulmonary edema associated with a medical treatment comprising inhalation of nitric oxide gas, said method comprising:

(a) performing echocardiography to identify~~identifying~~ a child in need of inhaled nitric oxide treatment for pulmonary hypertension, wherein the child is not ~~known to be~~ dependent on right-to-left shunting of blood;

(b) determining that the child identified in (a) has ~~pre-existing~~ left ventricular dysfunction and so is at particular risk of pulmonary edema upon treatment with inhaled nitric oxide; and

(c) excluding the child from inhaled nitric oxide treatment based on the determination that the child has ~~pre-existing~~ left ventricular dysfunction and so is at particular risk of pulmonary edema upon treatment with inhaled nitric oxide.

32. (Currently amended) The method of claim 31, wherein the child is a neonate~~has pulmonary hypertension~~.

33. (Currently amended) The method of claim 31, wherein step (b) comprises performing echocardiography and/or measuring the child's pulmonary capillary wedge pressure ~~the child has a pulmonary capillary wedge pressure that is greater than or equal to 20 mm Hg~~.

34. (Currently amended) A method of reducing the risk of occurrence of pulmonary edema associated with a medical treatment comprising inhalation of nitric oxide gas, said method comprising:

(a) ~~identifying a child~~carrying out a diagnostic process comprising measuring blood oxygen level, to identify a child as being in need of inhaled nitric oxide treatment for hypoxic respiratory failure, wherein the child is not ~~known to be~~ dependent on right-to-left shunting of blood;

(b) performing echocardiography and/or measuring pulmonary capillary wedge pressure to determine that the child has ~~determining by diagnostic screening that the child identified in (a) has pre-existing~~ left ventricular dysfunction and so is at particular risk of pulmonary edema upon treatment with inhaled nitric oxide; and

(c) excluding the child from treatment with inhaled nitric oxide based on the determination that the child has ~~pre-existing~~ left ventricular dysfunction and so is at particular risk of pulmonary edema upon treatment with inhaled nitric oxide.

35. (Currently amended) The method of claim 34, wherein the diagnostic process of step (a) further comprises performing ~~screening comprises~~ echocardiography.

36. (Currently amended) The method of claim 34, wherein the child is a neonate~~has pulmonary hypertension~~.

37. (Currently amended) The method of claim 34, wherein in step (b), the child's pulmonary capillary wedge pressure is measured and determined to be ~~the child has a pulmonary capillary wedge pressure that is~~ greater than or equal to 20 mm Hg.

38. (Currently amended) A method of treatment ~~reducing the risk of occurrence of pulmonary edema associated with medical treatment comprising inhalation of nitric oxide gas, said method~~ comprising:

(a) performing echocardiography to identify~~identifying~~ a plurality of children who are in need of inhaled nitric oxide treatment for pulmonary hypertension, wherein the children are not ~~known to be~~ dependent on right-to-left shunting of blood;

(b) determining that a first child of the plurality has ~~pre-existing~~ 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 ~~pre-existing~~ left ventricular dysfunction;

(d) administering the 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 ~~pre-existing~~ left ventricular dysfunction, so is at particular risk of pulmonary edema upon treatment with inhaled nitric oxide.

39. (Currently amended) The method of claim 38, wherein step (a) further comprises measuring blood oxygen levels in the first and second children and thereby determining that the first and second children are hypoxic ~~have pulmonary hypertension~~.

40. (Currently amended) The method of claim 38, wherein the second child has congenital heart disease.

41. (Currently amended) The method of claim 38, wherein step (b) comprises measuring the first child's ~~the first child has a~~ pulmonary capillary wedge pressure ~~greater than or equal to 20 mm Hg~~.

42. (Currently amended) The method of claim 38, wherein determining that the first child of the plurality has pre-existing left ventricular dysfunction and the second child of the plurality does not have pre-existing left ventricular dysfunction comprises performing echocardiography~~diagnostic screening~~.

43. – 45. (Canceled)

46. (New) A method of treatment comprising:

(a) identifying a plurality of children who are in need of inhaled nitric oxide treatment, wherein the children are not dependent on right-to-left shunting of blood;

(b) in the first child of the plurality, performing echocardiography and/or measurement of pulmonary capillary wedge pressure to determine that the first child of the

plurality has left ventricular dysfunction, so is at particular risk of pulmonary edema upon treatment with inhaled nitric oxide;

(c) in the second child of the plurality, performing echocardiography and/or measurement of pulmonary capillary wedge pressure to determine that the second child of the plurality does not have left ventricular dysfunction;

(d) administering the 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.

47. (New) The method of claim 46, wherein step (a) comprises performing echocardiography to determine that the first and second children have pulmonary hypertension.

48. (New) The method of claim 46, wherein step (a) comprises measuring blood oxygen levels in the first and second children and thereby determining that the first and second children are hypoxic.

49. (New) The method of claim 46, wherein the second child has congenital heart disease.

50. (New) The method of claim 46, wherein step (b) comprises measuring the first child's pulmonary capillary wedge pressure and determining that it is greater than or equal to 20 mm Hg.

51. (New) The method of claim 31, wherein the child's left ventricular dysfunction is attributable to congenital heart disease.

52. (New) The method of claim 31, wherein the child is determined to be at particular risk not only of pulmonary edema, but also of other Serious Adverse Events, upon treatment with inhaled nitric oxide, and the child is excluded from inhaled nitric oxide treatment based on the

determination that the child has left ventricular dysfunction and so is at particular risk not only of pulmonary edema, but also of other Serious Adverse Events, upon treatment with inhaled nitric oxide.

53. (New) The method of claim 34, wherein the left ventricular dysfunction is attributable to congenital heart disease.

54. (New) The method of claim 38, wherein the left ventricular dysfunction is attributable to congenital heart disease.

55. (New) The method of claim 46, wherein the left ventricular dysfunction is attributable to congenital heart disease.

56. (New) The method of claim 34, wherein the child is determined to be at particular risk not only of pulmonary edema, but also of other Serious Adverse Events, upon treatment with inhaled nitric oxide, and the child is excluded from inhaled nitric oxide treatment based on the determination that the child has left ventricular dysfunction and so is at particular risk not only of pulmonary edema, but also other Serious Adverse Events, upon treatment with inhaled nitric oxide.

57. (New) The method of claim 56, wherein the left ventricular dysfunction is attributable to congenital heart disease.

58. (New) The method of claim 38, wherein the left ventricular dysfunction of the first child is attributable to congenital heart disease.

59. (New) The method of claim 38, wherein the first child is determined to be at particular risk not only of pulmonary edema, but also of other Serious Adverse Events, upon treatment with inhaled nitric oxide, and the first child is excluded from inhaled nitric oxide treatment based on the determination that the first child has left ventricular dysfunction and so is

at particular risk not only of pulmonary edema, but also other Serious Adverse Events, upon treatment with inhaled nitric oxide.

60. (New) The method of claim 59, wherein the pre-existing left ventricular dysfunction of the first child is attributable to congenital heart disease.

61. (New) The method of claim 46, wherein the pre-existing left ventricular dysfunction of the first child is attributable to congenital heart disease.

62. (New) The method of claim 46, wherein the first child is determined to be at particular risk not only of pulmonary edema, but also of other Serious Adverse Events, upon treatment with inhaled nitric oxide, and the first child is excluded from inhaled nitric oxide treatment based on the determination that the first child has pre-existing left ventricular dysfunction and so is at particular risk not only of pulmonary edema, but also other Serious Adverse Events, upon treatment with inhaled nitric oxide.

63. (New) The method of claim 62, wherein the pre-existing left ventricular dysfunction of the first child is attributable to congenital heart disease.

REMARKS

Upon entry of the above amendment, claims 31-42 and 46-63 will be pending, claims 43-45 having been newly canceled and new claims 46-63 added. Claims 1-30 were canceled in a prior amendment. Support for the amended and new claims can be found throughout the specification, e.g., in paragraphs [0004]-[0006], [0014], [0017], [0018], [0023], [0027]-[0029], [0033], [0039], [0040], and [0042]. No new matter has been added.

As there are only four independent claims and 30 total claims (and no multiply dependent claims) in the application following entry of the above amendment, this application continues to qualify for special status under the provisions for Prioritized Examination (Track 1).

Statement of the Substance of Multiple Telephonic Interviews

On April 23, 2012, the undersigned spoke with Examiner Arnold by telephone. Examiner Arnold informed the undersigned that the Office action mailed January 31, 2012, would be withdrawn and replace with a new Office action. Applicants noted that a new Information Disclosure Statement and a Statement of Substance of the April 13, 2012, Interview had been filed, and requested that the Examiner review these filings prior to preparing a new Office action. The Examiner agreed to do so.

On April 30, 2012, the undersigned and Jonathan Provoost, Associate General Counsel of Ikaria, Inc. (the present application's assignee), spoke by telephone with Quality Assurance Specialist Julie Burke to follow up on the status of the proceedings following the April 13, 2012 Interview. QAS Burke informed applicants about various Office resources available to patent applicants, and suggested that applicants speak with SPE Brian Kwon and SPE Marjorie Moran, both of whom had participated in conversations with Examiner Arnold regarding the present application's claims.

Also on April 30, 2012, the undersigned spoke by telephone with SPE Brian Kwon. SPE Kwon noted that the Office actions in both the present case and a sister case (USSN 12/821,041) had been withdrawn and would be replaced with new Office actions.

Also on April 30, 2012, the undersigned spoke by telephone with SPE Marjorie Moran. SPE Moran confirmed that she had advised Examiner Arnold regarding how to apply the US Supreme Court's decisions concerning patent-eligible subject matter. SPE Moran provided some helpful guidance for applicants as to what kinds of amendments might be useful in overcoming a potential rejection for lack of patent-eligible subject matter. Applicants are grateful for the guidance, and have closely followed SPE Moran's advice in drafting the present amendments.

Comments Regarding Some of the Present Amendments

The amendment deletes the term "pre-existing" from the phrase "pre-existing left ventricular dysfunction" wherever that phrase appears in the claims.

The amendment deletes the term "known to be" from the phrase "the child is not known to be dependent on right-to-left shunting of blood," wherever that phrase appears in the claims.

The amendment adds at least one action step (e.g., "performing echocardiography") to each independent claim, as suggested by SPE Moran, in an effort to obviate any possible grounds for rejection for lack of patent-eligible subject matter under 35 USC § 101, and thereby expedite prosecution.

Amended claims 32 and 36 specify that the child is a neonate. Although applicants previously argued that the term "child" was defined in the specification at paragraph [0023] as excluding neonates, it is now believed that this is not precisely what paragraph [0023] says. The text reads: "As used herein, the term 'children' (and variations thereof) includes those being around 4 weeks to 18 years of age." Since the definition does not say that children under 4 weeks are excluded, it appears that "children" must logically include younger children, including neonates. (The paragraph [0023] definition would not logically include individuals who are over 18 years of age, as those are not normally classified as "children.")

Request for Panel Decision

Applicants respectfully request that SPE Kwon and QAS Burke continue to participate in the prosecution of the present application and assist Examiner Arnold in evaluating grounds for rejection and reaching a decision.

CONCLUSION

The excess claims fee in the total amount of $300 is being paid concurrently herewith on the Electronic Filing System (EFS) by way of Deposit Account authorization. Please apply all charges or credits to Deposit Account No. 06-1050, referencing the above attorney docket number.

Respectfully submitted,

Date: April 30, 2012

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EXHIBIT I

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	: James S. Baldassarre et al.	Art Unit	: 1613
Serial No.	: 12/821,020	Examiner	: Ernst V. Arnold
Filed	: June 22, 2010	Conf. No.	: 3179
Title	: Methods of Reducing the Risk of Occurrence of Pulmonary Edema in Children in Need of Treatment with Inhaled Nitric Oxide		

SUPPLEMENTAL REMARKS

This application has been granted special status under the prioritized examination (Track 1) program. An Office action was mailed January 31, 2012, setting a three-month deadline for response of April 30, 2012. As indicated in the Interview Summary mailed by the Office on April 24, 2012, the Examiner spoke by telephone with an assistant of the undersigned on April 20, 2012, stating that the Office action would be replaced with a new Office action. This message was confirmed by the Examiner in a telephone conference with the undersigned on April 23, 2012. In addition, the transaction history for this application on PAIR has two entries dated April 24, 2012: "Mail Notice of Withdrawn Action" and "Withdrawing/Vacating Office Action Letter." Applicants thus assume that there is no longer a pending deadline for response, and there will be no deadline for response until the new Office action is mailed and thereby resets a new deadline.

Applicants filed a Supplemental Amendment on April 30, 2012, with amendments intended to address potential issues under 35 U.S.C.§ 101 described by SPE Marjorie Moran in a telephone conference with the undersigned on April 30, 2012. The amendments are based on SPE Moran's helpful suggestions, so presumably fully address the potential issues described by her as arising under § 101. Applicants ask that the Supplemental Amendment be entered and considered prior to preparation of a new Office action.

As noted on page 10 of the Supplemental Amendment, applicants request that SPE Brian Kwon and QAS Julie Burke continue to participate actively in the prosecution of this application as a panel with Examiner Arnold. Applicants gratefully note that their perspective on the case has been very helpful to date in moving the case forward.

The remarks below are intended to assist the Examiner in understanding some technical points that appear to applicants to be a source of confusion in this case. The technical points are:

(1) the significance of the claim language "wherein the child is not dependent on right-to-left shunting of blood";

(2) the description of the child who is the subject of the claimed method; and

(3) the disclosures of the various references cited in the obviousness rejection set forth in the prior Office action dated January 31, 2012.

By resolving the apparent confusion regarding those three topics, applicants believe that these remarks should be very useful in moving the case forward efficiently.

(1) The significance of the claim language "*wherein the child is not dependent on right-to-left shunting of blood.*"

This language (or its equivalent "wherein the children are not dependent on right-to-left shunting of blood") appears in step (a) of each of the pending independent claims, as amended in the Supplemental Amendment filed April 30, 2012. It effectively narrows the scope of the claimed method by excluding outright some children from the set of children who are the subject of the method.

The term "dependent on right-to-left shunting of blood" is well understood in the medical art. See, for example, the use of this term in the 2007 INOmax prescribing information[1] cited in the January 31, 2012 Office action as the "INOmax insert" (page 2, left column, under "Contraindications"). The INOmax insert refers to a condition occasionally seen in neonates born with an absent or nonfunctional left ventricle -- the ventricle that normally pumps blood into the systemic circulation. Ordinarily, such a neonate will die immediately from a lack of systemic circulation. Under certain circumstances, however, these neonates may survive: i.e., when two other independent conditions both exist concurrently with the nonfunctional left ventricle: (i) an open (patent) ductus arteriosus, and (ii) an abnormally high level of pulmonary vascular resistance (routinely arising from pulmonary hypertension). When both of these

[1] Also commonly referred to as the "package insert" or "PI".

conditions exist concurrently in a neonate who lacks a functional left ventricle, the neonate's right ventricle (which normally pumps blood only into the lungs) can take over the left ventricle's normal function of supplying blood flow to the systemic circulation. The right ventricle would have no outlet into the systemic circulation unless the infant's ductus arteriosus, a vascular connection between the pulmonary artery (which exits the right ventricle) and the aorta (which feeds the systemic circulation), remains open after birth. The ductus arteriosus normally closes at birth. If instead it remains open in a neonate who has no functioning left ventricle, the ductus arteriosus will provide a conduit for some of the blood pumped by the right ventricle to shunt into the systemic circulation rather than taking its normal route into the lungs. This is termed a right-to-left shunt through a patent ductus arteriosus (PDA). If the neonate concurrently has pulmonary hypertension, this means relatively less blood goes from the right ventricle into the vasoconstricted lungs, thereby allowing more blood to shunt from the right ventricle through the PDA. In some cases, enough blood shunts through the PDA to sustain the systemic circulation. If the amount of blood flowing from the right ventricle through the PDA into the systemic circulation is sufficient to maintain life, and if the neonate's left ventricle is so severely dysfunctional that, absent this shunt through the PDA, the neonate would die from an inadequate systemic circulation, the neonate is said to be "***dependent*** on right-to-left shunting of blood." The reason this dependence on right-to-left shunting of blood has always been a contraindication on the INOmax® package insert since the product was first marketed is because it was known in the art that a patient who has pulmonary hypertension and is dependent on right-to-left shunting of blood, and who is treated with inhaled nitric oxide to open up the pulmonary blood vessels and thereby allow more blood to flow through the lungs, can suffer a catastrophic loss of the right-to-left blood flow through the PDA on which the patient depends for life.

There are many other situations in which a patient who is a candidate for treatment with inhaled nitric oxide (e.g., because the patient has pulmonary hypertension) exhibits a right-to-left shunt, a left-to-right shunt, or even a bi-directional shunt. Such a shunt can be through a PDA; through a hole between the right and left atria, termed the foramen ovale; or through a hole in the septum (wall) between the left and right ventricles, termed a ventricular-septal defect. Except for the situation described above with the particular combination of conditions specified above (i.e., nonfunctional left ventricle, pulmonary hypertension, and a PDA through which blood shunts

right-to-left in a volume that is sufficient to maintain the systemic circulation despite the nonfunctional left ventricle), the patient is not "dependent" on any of these shunts—i.e., his/her life does not depend on maintaining the shunt. In fact, it is more common that a shunt is harmful rather than helpful to the patient, because it diverts blood away from its normal path through the right side of the heart to the lungs (where it is oxygenated), then into the left side of the heart, and from there into the systemic circulation for delivery to all parts of the body. For example, a right-to-left shunt at the atrial level, i.e., through the foramen ovale, means some of the deoxygenated blood entering the right atrium is shunted into the left atrium instead of taking its normal path into the right ventricle and then into the lungs. In such a patient, the "shunted" deoxygenated blood then passes from the left atrium into the left ventricle and is pumped by the left ventricle into the systemic circulation, still in its deoxygenated state, leaving the infant chronically poorly oxygenated. Far from being "dependent" on this right-to-left-shunt through the foramen ovale, the patient would be much better off without it.

The articles cited by the Examiner in the obviousness rejection described in the January 31, 2012 Office action discuss in various contexts right-to-left shunts and left-to-right shunts (sometimes referring to the shunt as "exclusively" right-to-left or "exclusively" left-to-right). These shunts may occur at an open foramen ovale, at a PDA, or at a ventricular-septal defect. The sole situation in which the patient is "dependent" on a shunt is the one described above, where the patient has a combination of pulmonary hypertension, a severely dysfunctional or absent left ventricle, and a right-to-left shunt through a PDA. (As described on page 452, left column, of Atz & Wessel, Seminars in Perinatology 1997, 21(5): 441-455 (one of the references cited in the January 31, 2012 Office action), such a patient may also have, in addition to that combination of conditions, a left-to-right shunt through an open foramen ovale; such a patient is still characterized as "dependent on a right-to-left shunt" because of the critical role played by the right-to-left shunt through the PDA.) Characterizing a shunt as "exclusively" right-to-left or "exclusively" left-to-right means that the blood flows only in the indicated direction through that shunt. It does not mean, and does not even imply, that the patient is "dependent" on the shunt. In fact, most patients who have a shunt that is exclusively in one direction are harmed by the shunt, far from being "dependent" on it.

Applicants hope that the above discussion helps to clarify the significance of the word "dependent" in the claim language "dependent on right-to-left shunting of blood."

(2) The description of the child who is the subject of the claimed method.

During the April 13, 2012 Interview, QAS Burke mentioned that the negative limitations of claim 31 made the claim somewhat difficult to parse. Applicants have attempted to simplify the claims by omitting the words "known to be" in step (a) of each independent claim. (See the Supplemental Amendment filed April 30, 2012.) Claim 31 is a drawn to a method of reducing the risk of occurrence of pulmonary edema associated with a medical treatment comprising inhalation of nitric oxide gas, where the method includes identifying a narrowly defined category of children who are in need of nitric oxide treatment but who are at particular risk of pulmonary edema from that treatment, and excluding from the treatment any child who falls into that defined category of at-risk patients. It is important to note that the prior art was unaware that any children were at particular risk of pulmonary edema when treated with inhaled nitric oxide. The prior art did know that some children (i.e., neonates who are dependent on right-to-left shunting of blood) were at risk of systemic hypotension when treated with inhaled nitric oxide, but this risk has nothing to do with a risk of pulmonary edema and does not predict a risk of pulmonary edema. *Thus, the claim would be novel and nonobvious regardless of how the category of children to be excluded from the treatment is defined in the claim.* Since the basis for the invention was the discovery that children who have left ventricular dysfunction are surprisingly at risk for pulmonary edema when they are treated with inhaled nitric oxide, the claims include a limitation that the child to be excluded from treatment due to this risk is determined to have left ventricular dysfunction. In addition to this limitation on the scope of the claim, applicants have chosen to narrow the scope even further by explicitly requiring that the category of children covered by the claim not include those who are dependent on right to left shunting of blood.

Applicants hope that this discussion of the claims will help the Examiner understand the nature of the claims and the effect of the various limitations on claim scope.

(3) The disclosures of the various references cited in the obviousness rejection set forth in the prior Office action dated January 31, 2012.

The comments below address the following six references that were cited by the Office in support of the obviousness rejection in the January 31, 2012 Office action. The below comments focus on what applicants believe are misinterpretations of the references expressed in that Office action. Applicants realize that Office action has been withdrawn and so the prior obviousness rejection is presently moot, but are concerned that the same references may be cited in a new Office action. Thus, to facilitate efficient prosecution, applicants would like to clarify for the Examiner's benefit what those references actually say regarding the points raised in the Office action. The references considered below are:

Fraisse et al., Cardiol Young 2004; 14:277-283;

Atz & Wessel (mentioned above);

Kinsella et al., The Lancet 1999; 354:1061-1065;

Loh et al., Circulation 1994; 90:2780-2785;

Beghetti et al., J. Pediatrics 1997; page 844;

Henrichsen et al., Journal of Pediatrics 1996; 129(1):183; and

Ichinose et al., Circulation 2004; 109:3106-3111.

Fraisse et al.

Applicants first point out that the senior author on Fraisse et al. is David L. Wessel, M.D. Dr. Wessel is also the senior author of Atz & Wessel. His views about the nonobviousness of the present invention are set forth in the Declaration of David L. Wessel, M.D. under 37 CFR § 1.132 submitted with applicants' Reply filed December 27, 2011 (the 12/27/11 Reply), and are discussed in detail in the 12/27/11 Reply. In brief, Dr. Wessel, who was presumably fully aware of both of these articles that he co-authored, says that he did not expect that children who have pulmonary hypertension and LVD would be at increased risk of pulmonary edema upon inhalation of nitric oxide until after the INOT22 clinical trial had proven, to his surprise, that this was indeed a real risk. That trial concluded long after Fraisse et al.'s 2004 publication date and Atz & Wessel's 1997 publication date. *This is a substantial clue that the Examiner's interpretation of these two articles as disclosing such a risk is incorrect.* That the Examiner's

interpretation is indeed incorrect is borne out by a careful parsing of what Fraisse et al. and Atz & Wessel actually say. Applicants attempted to do that with respect to Atz & Wessel in the 12/27/11 Reply, and with respect to Fraisse et al. in the 4/13/12 Interview. Fraisse et al. is addressed in more detail here.

Fraisse et al. performed a retrospective analysis of echocardiographic features of newborns with persistent pulmonary hypertension who had been randomized to receive inhaled nitric oxide or other therapy in a previous clinical trial. The purpose of the Fraisse et al. analysis was to see whether these features could be used as a predictor of what the clinical trial had defined as a successful response to inhaled nitric oxide therapy. *See*, abstract. The clinical trial had defined a successful response to inhaled nitric oxide therapy as occurring when the patient survived without having to be placed on an alternative therapy (extracorporeal membrane oxygenation, "ECMO") to improve oxygenation. Fraisse et al. says nothing about pulmonary edema nor any other adverse events attributable to treatment with inhaled nitric oxide, except for noting that one patient whose systemic circulation was dependent on a right-to-left shunt through an open ductus arteriosus[2] experienced "haemodynamic deterioration" when inhaling nitric oxide (see page 281, upper left column). That haemodynamic deterioration was likely systemic hypotension,[3] i.e., not related to pulmonary edema.

The January 31, 2012 Office action at pages 4-5 characterizes Fraisse et al. in part as follows:

> Fraisse et al. teach that ***a left to right shunting of blood*** increases the risk of failing to respond to iNO including a patient with severe left ventricular dysfunction (Abstract and page 281 upper left column).

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[2] The patient also reportedly had "an exclusively left-to-right shunt at the atrial level." In other words, the foramen ovale was open and allowed blood to flow in one direction, from the left atrium into the right atrium (i.e., left to right). In a patient who is dependent on a right-to-left shunt through a PDA, a left-to-right shunt through the foramen ovale has two effects: (1) it provides an outlet out of the left atrium for blood entering the left atrium from the lungs, thereby relieving pressure on the dysfunctional left ventricle; and (2) it allows oxygenated blood from the left atrium to mix with the deoxygenated blood being pumped from the right atrium into the right ventricle, which can pump it through the ductus arteriosus into the systemic circulation—i.e., it increases the oxygenation level of the blood entering the systemic circulation through the PDA.

[3] Elsewhere (page 280, top of right column) Fraisse et al. uses the term "haemodynamic instability" to mean "hypotension."

The Fraisse et al. abstract and page 281, upper left column, does teach that left to right shunting of blood at the atrial level (i.e., through an open foramen ovale)[4] increased the risk of *failing to respond* to inhaled nitric oxide. Further, the cited part of Fraisse et al. at page 281, upper left column, does describe a patient with left to right shunting of blood at the atrial level who also had severe left ventricular dysfunction and who *failed to respond* to inhaled nitric oxide. However, the significance of those observations to the present claims is not clear, since the claims are not about identifying patients who will respond, or fail to respond, to inhaled nitric oxide. Rather, the claims are about reducing the risk of pulmonary edema. Pulmonary edema is a side effect that would be triggered by treatment with inhaled nitric oxide only when a patient's pulmonary hypertension responds well to the treatment—i.e., when the treatment is effective in relaxing the constricted pulmonary blood vessels, permitting an increased volume of blood to flow through the lungs and into the left side of the heart. It appears that the Examiner may have confused the concept of *failure to respond* to a given treatment with the concept of *adverse events* caused by the treatment. As noted by Dr. Greene during the April 13, 2012 Interview, these are two entirely different concepts.

The Office action continues:

> Thus the patient is not known to be dependent on right to left shunting of blood and the patient had pre-existing left ventricular dysfunction before administration of iNO was performed.

The individual patient to which this sentence refers cannot be characterized, as the Office does, as "not known to be dependent on right to left shunting of blood." In fact, the description of that particular patient at page 281, upper left column, of Fraisse et al. says essentially the opposite:

> This last patient [who presented with persistent pulmonary hypertension], with an exclusively left-to-right shunt at the atrial level, also had a right-to-left ductal shunt. His left ventricular function was severely depressed, with echocardiographic evidence of a right ventricular dependent circulation. (Emphasis added)

[4] A shunt at the "atrial level" is a shunt through the foramen ovale, a hole between the left atrium and right atrium (chambers of the heart). The word "atrial" should not be confused with the similar word "arterial", which refers to arteries and not chambers of the heart.

A "right-to-left ductal shunt" is a right-to-left shunt through a patent ductus arteriosus (i.e., PDA). A "right ventricular dependent circulation" means, of course, that the right ventricle had taken over the job of supplying blood to the systemic circulation since the left ventricle's function was severely depressed. Fraisse et al. thus describes this neonatal patient as showing evidence of a combination of five conditions:

(i) persistent pulmonary hypertension;

(ii) an exclusively left-to-right shunt at the atrial level (i.e., through an open foramen ovale);

(iii) a right-to-left ductal shunt (i.e., through a PDA);

(iv) severely depressed left ventricular function (i.e., left ventricular dysfunction, or LVD); and

(v) evidence of a right ventricular dependent circulation (i.e., since his left ventricle was not functioning properly, the only way this patient survived was because his right ventricle had taken over the job of pumping blood into the systemic circulation, and that occurred only because the ductus arteriosus was open and permitted blood to flow from the pulmonary artery through the PDA into the aorta). This patient appears to fit the classic description of a neonatal LVD patient whose systemic circulation is dependent on right-to-left shunting of blood through a PDA, and who therefore should not be given inhaled nitric oxide because of the risk of systemic circulatory collapse, i.e., systemic hypotension. (See, e.g., the description of such newborns provided on page 452 of Atz & Wessel, as described in detail in applicants' Reply filed December 27, 2011, at pages 12-15.) Indeed, Fraisse et al. describes this particular patient as having "responded poorly to inhalation of nitric oxide, with persistence of hypoxaemia and haemodynamic deterioration." The "haemodynamic deterioration" was likely systemic hypotension induced by diversion of blood into the lungs and away from the PDA upon which the patient's systemic circulation depended, severely reducing the flow of blood into the systemic circulation. Applicants therefore submit that the Examiner is mistaken in asserting that this patient "is not known to be dependent on right to left shunting of blood." That plainly is not the case.

The January 31, 2012 Office action continues by pointing to Table 2 of Fraisse et al. as giving clinical data and hemodynamic characteristics of 44 neonates who started treatment with inhaled nitric oxide. See, the January 31, 2012 Office action at page 5. No explanation is provided as to what, if anything, in this table is considered to be relevant to the claims. Applicants note that, according to Table 2, three of the patients treated with inhaled nitric oxide

reportedly had "moderately or severely depressed" left ventricular function. The table categorizes one of these as a "responder" (i.e., inhaled nitric oxide was effective) and two as "non-responders" (i.e., inhaled nitric oxide was not effective). Five other patients who were classified as having "mildly depressed" left ventricular function all were "responders." The table does not report any adverse events (pulmonary edema or otherwise) caused by the treatment in any patients. It therefore seems irrelevant to the claims, except as a possible *teaching-away*.

The January 31, 2012 Office action then quotes extensively from pages 281 and 282 of Fraisse et al., without comment except to say on page 7: "The Examiner interprets 'reduced left ventricular compliance' to be a dysfunction of the left ventricle such that compliance is reduced." Absent the Examiner's views of why the lengthy quoted text is relevant to the claims, applicants are uncertain how to respond. *Below is a brief summary of the text that the January 31, 2012 Office action quoted from pages 281 and 282 of Fraisse et al., with applicants' comments.*

The text from page 281 of Fraisse et al. is quoted on page 5 of the January 31, 2012 Office action. It begins with a general description of how echocardiography is used in evaluating newborns with persistent pulmonary hypertension. It then discusses the authors' findings regarding left and right ventricular function in the patients included in the study, including an observation that some patients had significant depression of left ventricular function.

The text from page 282 appears on pages 6-7 of the Office action. It was extracted from a paragraph of Fraisse et al. that begins by noting that several studies have shown that inhaled nitric oxide is effective in improving oxygenation and reducing the need for ECMO in newborns with persistent pulmonary hypertension. The quoted paragraph then says that the results of the present study indicate that those newborns with an exclusively left-to-right shunt across the atrial septum (i.e., through an open foramen ovale) have an increased risk of failing to respond to nitric oxide. *(Note that the authors did not assess side effects of the treatment, but rather only response or failure to respond.)* Fraisse et al. discuss the phenomenon of left-to-right shunting across the atrial septum in the context of a predominantly left-to-right ductal shunt and <u>normal biventricular function</u>, saying that "[in] this subgroup of patients, systemic oxygenation is significantly less improved by inhalation of nitric oxide"—i.e., the treatment is not as effective as it is in other patients. (Note that this particular discussion in Fraisse et al. refers to patients

with "normal biventricular function," meaning that their left and right ventricles both function normally, so there is plainly no LVD; furthermore, it is about effectiveness of the treatment, not adverse events caused by the treatment. It therefore appears to be irrelevant to the present claims.)

According to the authors, left to right shunting across the atrial septum may also occur in another context: a patient with decreased left ventricular compliance may have increased left atrial pressure, and this can produce "a resultant left-to-right shunt across the oval foramen." In other words, the increased pressure built up in the left atrium because the left ventricle has decreased compliance can cause blood to escape the left atrium through the open foramen ovale into the right atrium (i.e., left to right). In this situation, the open foramen ovale acts like a pressure relief valve for the left atrium. Note that there is no suggestion that, instead of escaping through the foramen ovale, the blood would back up into the pulmonary vessels and produce pulmonary edema; rather, the only disclosed result of the increased left atrial pressure is a left to right shunt of blood from the left atrium into the right atrium. This shunt would presumably serve to relieve at least some of the left atrial pressure, leaving one of skill in the art with no reason to expect that pulmonary edema would develop. Thus, this part of Fraisse et al. also appears to *teach away* from the presently claimed methods—and certainly does not support the rejection.

The reference goes on to explain what might cause decreased left ventricular compliance in patients with persistent pulmonary hypertension of the newborn. The causes listed by Fraisse et al. include adverse interaction between the ventricles (i.e., the adjacent left and right ventricles don't interact in a normal way, typically due to an enlarged right ventricle that is filled with blood at abnormally high pressure as it works hard to push blood into the constricted lung blood vessels); a leftward shift of the ventricular septum (i.e., the septum or wall shared by both ventricles is pushed "leftward" into the left ventricle's space by the enlarged right ventricle); decreased left ventricular diastolic filling (there is an inadequate volume of blood flowing from the vasoconstricted lungs into the left side of the heart, and less room in the left ventricle because of interference by the right ventricle, adding up to decreased filling of the left ventricle); and left ventricular systolic (emptying) dysfunction due to decreased preload (i.e., the "preload," or pressure exerted on the left ventricle by the blood present in the left atrium, is decreased due to

the decreased flow of blood from the lungs into the left atrium and/or due to an open foramen ovale that permits blood to leak out of the left atrium into the right atrium; this decreased preload can make the left ventricle less efficient at contracting), hypoxaemia (low oxygenation), and acidosis (increased acidity of the blood). Fraisse et al. then describe what happens when left ventricular systolic (emptying) function is severely depressed in newborns with persistent pulmonary hypertension: the right ventricle takes over, providing blood flow to the systemic circulation by pumping blood through the patent (open) arterial duct (i.e., the PDA). As taught by Fraisse et al. on page 282, top of right column, treating such a patient with inhaled nitric oxide "may not give the desired clinical response, because the blood flowing across the duct is redistributed away from the systemic circulation towards the lungs, decreasing post-ductal systemic output, and increasing the left atrial pressure." Thus, Fraisse et al. points out that neonates whose systemic circulation is dependent on a right-to-left shunt through the open ductus are expected to suffer a loss of "post-ductal systemic output" (i.e., flow from the right side of the heart through the open ductus into the systemic circulation) if they are treated with inhaled nitric oxide—i.e., they may end up with life-threatening systemic hypotension. This is, of course, the well-known contraindication for inhaled nitric oxide in patients who are dependent on a right-to-left shunt, a set of patients explicitly outside the category of children defined in part (a) of each of the independent claims. This discussion by Fraisse et al. therefore has nothing to do with the category of patients to whom the claimed method applies. Furthermore, ***it has nothing to do with pulmonary edema.*** Applicants note for the record that Fraisse et al.'s reference to "increasing the left atrial pressure" as one of the effects of inhaled nitric oxide in these patients does not imply that pulmonary edema would result. For example, if, prior to the treatment, the left atrial pressure was below normal (as may occur when pulmonary hypertension has reduced the blood flow into the left atrium, and as confirmed by the reference in the quoted text to "decreased preload"[5]), the increase in left atrial pressure may just bring the pressure up to a normal range. Thus, the observation about "increasing the left atrial pressure" does not in itself imply any pathology. Further, the cite provided by Fraisse et al. as support for the statement

[5] Fifth line from the bottom of page 5 of the Office action. "Preload" in this context is the pressure exerted on the left ventricle by the volume of blood present in the left atrium. "Decreased preload" means the pressure is below normal.

about "decreasing post-ductal systemic output, and increasing the left atrial pressure" is Henrichsen et al., *J. Pediatr.* 1996; 129:183, a case study of a single infant who was reported to be dependent on a right-to-left shunt and who suffered systemic hypotension (not pulmonary edema) after being treated with inhaled nitric oxide. Applicants submit that the sole relevance of this part of Fraisse et al. is as a description of patients who are dependent on a right-to-left shunt at the ductus arteriosus, a category of patients explicitly excluded from the category of children that is the subject of all of the claims. ***Thus, Fraisse et al.'s teaching regarding what occurs in such neonates is entirely irrelevant to the claimed methods.***

The final passage that the January 31, 2012 Office action quotes from Fraisse et al. is taken from the last paragraph on page 282. The sentence fragment "are at increased risk of death" that begins the quoted section is derived from a sentence that reads in full: "A pure right-to-left ductal shunt identified the patients who are at increased risk of death." This "risk of death" was not attributed to the treatment *per se*, but rather to the underlying condition. (*See*, e.g., page 281, right column, second full paragraph.) Further, Fraisse et al. does not suggest that the patients found to be at increased risk of death had LVD. That part of the quoted text is therefore irrelevant to the present claims. The quoted section then says, "A pure left-to-right ductal shunt tends to be associated with greater need for extracorporeal membrane oxygenation, and should prompt cautious re-evaluation of the indication for further treatment aimed at increasing pulmonary vasodilation." Applicants cannot see how this statement is at all pertinent to the presently claimed methods. It does not suggest that the patients with the left-to-right ductal shunt had LVD, and it concerns the lack of efficacy of inhaled nitric oxide in patients with a left-to-right ductal shunt--not adverse events (pulmonary edema or anything else) attributable to this treatment. If the Examiner intends to cite Fraisse et al. (and these statements of Fraisse et al. in particular) in a new obviousness rejection, he is respectfully asked to clarify why he believes these statements of Fraisse et al. to be relevant. They appear to be as irrelevant as the other Fraisse et al. text discussed above.

In sum, Fraisse et al. is concerned with using echocardiography to identify neonates in whom inhaled nitric oxide is less likely to be efficacious—i.e., who died from their underlying condition despite the inhaled nitric oxide treatment, or who had to be put on ECMO in an effort to improve their oxygenation and keep them alive. Though some of the neonates in the trial

analyzed by Fraisse et al. did have evidence of LVD, the authors do not link that observation to any identified risk—or even a reduction in efficacy--of the treatment, except for one patient in whom LVD was combined with dependence on a right-to-left shunt at the ductus arteriosus, so who is explicitly outside the population of patients defined as the subject of the present claims. In fact, the utter lack of any mention by Fraisse et al. of an actual or expected increased incidence of pulmonary edema in *any* subset of the neonates in the study following treatment with inhale nitric oxide suggests that no such increased incidence was expected, much less found. Further, Fraisse et al. observed that increased left atrial pressure due to decreased left ventricular compliance was associated with an escape valve of sorts: a flow of blood from the left atrium to the right atrium through the open oval foramen.[6] ***Thus, Fraisse et al.'s only apparent relevance to the present claims is as a teaching away.***

If the Examiner disagrees with this assessment of the Fraisse et al. article, he is asked to explain why.

Atz & Wessel

The alleged teachings of Atz & Wessel are described on pages 7-8 of the January 31, 2012 Office action:

> Atz et al. warn that sudden pulmonary vasodilation may produce pulmonary edema (page 452, left column). Atz et al. teach that: "Caution should be exercised when administering NO to patients with severe left ventricular dysfunction and pulmonary hypertension." (page 452, left column).... Atz et al. continues with: "Therefore, in newborns with severe left ventricular dysfunction, predominantly left to right shunting at the foramen ovale and exclusively ***right to left shunting*** at the ductus arteriosus, ***NO should be used with extreme caution, if at all***. We and others have reported ***adverse outcomes*** in this circumstance." (page 452, left column) (Examiner added emphasis). Therefore it is known in the art that patients who had pre-existing LVD treated with NO for any duration may experience adverse outcomes.... Thus, Atz et al. fairly teaches excluding patients which include pediatric patients with left ventricular dysfunction from inhaled NO treatment because the Examiner interprets "if at all" to mean no treatment and hence exclusion from treatment. The left ventricular dysfunction is intrinsically pre-existing.
>
> To summarize, the methods disclosed by Atz et al. are interpreted to mean:

[6] Page 282, left column, last paragraph.

- identifying a patient eligible for NO treatment;
- diagnosing/identifying if the patient has left ventricular dysfunction;
- excluding that patient with left ventricular dysfunction from treatment with NO but treating the patient with NO for other conditions discussed by Atz et al. with inhalation of NO thereby reducing the risk of adverse events associated with the medical treatment.

This characterization of Atz & Wessel is exactly the same as the one presented on pages 10-11 of the previous Office action dated June 27, 2011 (the "6/27/11 Office action"). Applicants' reply to the 6/27/11 Office action (the 12/27/11 Reply) included a detailed rebuttal of the Examiner's characterization of Atz & Wessel, pointing out that the Examiner's interpretation of the Atz & Wessel reference was far broader than what it really says. See pages 10-17 of the 12/27/11 Reply. Applicants' arguments were not simply opinion, but rather were supported by a careful parsing of the crucial paragraph on page 452 of the reference as well as by factual evidence submitted with the 12/27/11 Reply, and were intended to assist the Examiner in coming to a clearer understanding what the reference actually communicated to those of skill in the art. Unfortunately, rather than address applicants' arguments and evidence about what this reference says, either agreeing with them or pointing out any perceived errors or deficiencies in applicants' submission so that applicants can respond, the January 31, 2012 Office action simply repeats, word for word, the prior overbroad characterization of the reference, dismissing applicants' entire submission regarding Atz & Wessel as "moot." Applicants fail to see how guidance as to how to interpret a reference's disclosure can possibly be "moot" if the reference is still being cited for exactly the same alleged disclosure. Forcing applicants to re-present the same arguments and evidence already of record, to address exactly the same points addressed by applicants' prior remarks, does not advance prosecution in an efficient way, wasting time, money and the Office's resources, and delaying a resolution in this case. Applicants request that the Examiner provide a substantive response, either accepting applicants' positions or explaining why, in the Examiner's view, the facts do not support these positions.

Rather than re-submit the entire eight pages of arguments (and related exhibits) about the Atz & Wessel reference submitted in the 12/27/11 Reply, applicants direct the Examiner's

attention to pages 10-17 of the 12/27/11 Reply and to Exhibits A-C submitted with that reply. In those eight pages, supported by Exhibits A-C, applicants explained that the broad statement at the beginning of the pertinent paragraph of Atz & Wessel must be read in the context of the rest of the paragraph, which explains that the entire universe of LVD patients at risk from treatment with inhaled nitric oxide is limited to the two defined patient groups well known in the art to be at risk: adults with ischemic cardiomyopathy (who are at risk of pulmonary edema) and newborns who are dependent on a right-to-left shunting of blood (who are at risk of systemic circulatory collapse). Atz & Wessel did not suggest that inhaled nitric oxide treatment might pose a particular risk to any other patient group (whether with or without LVD), and certainly did not suggest that the treatment might trigger pulmonary edema in anyone but adults with LVD due to ischemic cardiomyopathy. The January 31, 2012 Office action's purported summary of Atz & Wessel as implying that all patients (including all pediatric patients) with LVD should be excluded from treatment with inhaled nitric oxide is simply wrong. Further, the risk specified in the claims is specified as being pulmonary edema, a risk that Atz & Wessel discussed solely in the context of adult patients—not the children specified in the claims. There was no recognition whatsoever in Atz & Wessel, or in any of the other cited art, that infants and children with LVD might be at risk of pulmonary edema upon treatment with inhaled nitric oxide. Dr. Wessel's declaration (Exhibit C submitted with the 12/27/11 Reply) establishes that in fact his Atz & Wessel article did not disclose that pediatric LVD patients--other than those dependent on a right-to-left shunt, who are known to be at risk of systemic hypotension, not pulmonary edema--were at any risk from the treatment, and that he was surprised when the new risk was discovered in the course of the INOT22 clinical trial that he helped design in 2006. As noted by Dr. Wessel, if he had expected children with LVD who are not dependent on a right-to-left shunt to be at risk from the treatment, he would not have allowed them to be included in the clinical trial. The Examiner is asked to give due consideration to the detailed explanation of Atz & Wessel provided on pages 10-17 of the 12/27/11 Reply, and to the factual evidence submitted in support thereof, and to acknowledge that the description of this reference provided in the last two Office actions does not accurate reflect what the reference discloses.

Kinsella et al.

As with the Atz & Wessel reference, the January 31, 2012 Office action's characterization of Kinsella et al. at page 9 is word-for-word identical to the way Kinsella et al. was characterized in the 6/27/11 Office action. Also as with the Atz & Wessel reference, applicants' discussion of Kinsella et al. at pages 18-20 of the 12/27/11 Reply, though entirely relevant to how this reference is described and cited in the present rejection, was dismissed as "moot" by the January 31, 2012 Office action, rather than being addressed on the merits. Applicants ask the Examiner to give due consideration to the detailed discussion of Kinsella et al. provided at pages 18-20 of the 12/27/11 Reply, including the factual evidence (Exhibits C and D) cited in support of that discussion. In brief, that discussion establishes that one of ordinary skill in the art would have viewed Kinsella et al. as irrelevant to the present claims. It is noted that the Examiner has not even attempted to rebut applicants' position.

Loh et al.

At risk of sounding repetitive, applicants point out that the January 31, 2012 Office action's characterization of yet another reference--Loh et al.--is again word-for-word identical to the way this reference was characterized in the 6/27/11 Office action. See pages 9-10 of the January 31, 2012 Office action. As with applicants' discussion of Atz & Wessel and Kinsella et al., applicants' discussion of Loh et al. at pages 20-21 of the 12/27/11 Reply, though entirely relevant to how this reference is described and cited in the present rejection, was inappropriately dismissed as "moot" by the January 31, 2012 Office action rather than being addressed on the merits. Applicants ask the Examiner to give due consideration to the detailed discussion of Loh et al. provided at pages 20-21 of the 12/27/11 Reply, including the fact that Loh et al. is solely about adult patients who have an importantly different form of LVD than that typically found in children. That is, the adult form of LVD that concerns Loh et al. (diastolic LVD) renders the left ventricle stiff and unable to stretch readily to accept blood, while childhood LVD is generally characterized by a weak, flabby left ventricle that stretches easily but has weak

contractions.[7] These assertions are supported by factual evidence submitted with the 12/27/11 Reply, evidence that has not yet been considered on the record by the Examiner. Applicants have explained in detail in the 12/27/11 Reply why one of ordinary skill in the art would not have expected the results in adults (as reported by Loh et al.) to be duplicated in children, citing factual evidence to support this position. The Examiner is asked to address applicants' position and evidence on the record, rather than again dismissing it as "moot."

Beghetti et al. and Henrichsen et al.

Beghetti et al. is a newly cited brief Letter to the Editor in the Journal of Pediatrics, written in response to a prior Letter to the Editor in the same journal entitled "Inhaled nitric oxide can cause severe systemic hypotension" (Henrichsen et al., J. Pediatrics 129:183,1996; listed as "pertinent to applicant's disclosure" on page 18 of the January 31, 2012 Office action). In order to put Beghetti et al.'s comments into context, it is necessary to review what Henrichsen et al. said.

Henrichsen et al. is a case study of a newborn baby who was given inhaled nitric oxide as a treatment for persistent pulmonary hypertension. The baby is said to have had severe left ventricular dysfunction and a PDA, and was diagnosed as being "dependent on the right-to-left shunt through the PDA." Because of that dependence on right to left shunting of blood, the baby described by Henrichsen et al. (and discussed after-the-fact by Beghetti et al.) does not meet the criteria of the child described in step (a) of each of the independent claims, all of which limit the child or children to one who "is not dependent on right-to-left shunting of blood." Treatment of Henrichsen et al.'s patient with inhaled nitric oxide "resulted in an immediate fall in the mean systemic arterial blood pressure from 48 to 35 mmHg, which reversed when NO therapy was discontinued," i.e., the baby experienced systemic hypotension upon inhalation of NO.

[7] The January 31, 2012 Office action at page 7 points to page 282 of Fraisse et al. as evidence that children can have "reduced left ventricular compliance." Dr. Greene addressed this phenomenon in the April 13, 2012 Interview. According to Dr. Greene, the "reduced left ventricular compliance" to which Fraisse et al. referred is a temporary situation induced by the expanded, overworked right ventricle, which pushes against the left ventricle and reduces its "compliance"—i.e., its ability to fill. When such a patient is treated with inhaled nitric oxide to open up the constricted pulmonary blood vessels, blood flows out of the right ventricle into the lungs, thereby reducing the pressure and size of the right ventricle so that it no longer interferes with the left ventricle. The left ventricle then recovers its normal level of compliance and is able to handle the increased flow from the lungs.

According to Henrichsen et al., "This hypotensive episode was thought to have been caused by the NO's reversing the right-to-left shunt through the PDA on which the systemic circulation depended." In other words, the baby's systemic circulation was dependent on a right-to-left shunt through a PDA and was adversely affected, resulting in hypotension, when inhaled nitric oxide reduced the patient's pulmonary hypertension. This of course is exactly what is now well known to occur in neonates who are dependent on right-to-left shunting of blood, and is why such neonates are contraindicated for treatment with inhaled nitric oxide. Henrichsen et al. says nothing about inhaled nitric oxide's having caused any problems other than systemic hypotension. ***In particular, there is no mention of pulmonary edema.*** As discussed by Dr. Greene during the April 13, 2012 Interview, pulmonary edema and systemic hypotension are entirely different and conceptually inconsistent conditions, one being treated by decreasing fluids and the other being treated by increasing fluids.

Beghetti et al. read the case study published by Henrichsen et al. and offered their own interpretation of what may have been occurring in the infant. They dismissed Henrichsen et al.'s view that the baby was dependent on a right-to-left shunt and suggested that the systemic hypotension exhibited upon treatment with inhaled nitric oxide was instead due to further left ventricular failure caused by "overfilling"—i.e., the left ventricle was even less able to pump than it was before the treatment began, thereby reducing the blood flow out of the left ventricle and contributing to systemic hypotension. Though Beghetti et al. appeared perfectly willing to speculate about what might have been occurring, despite not having seen the baby or any data other than that provided in Henrichsen et al.'s letter, ***they do not even suggest that the proposed "overfilling" of the left ventricle might have precipitated pulmonary edema in the baby***. Beghetti et al. simply offered an alternative explanation for the observed fall in systemic blood pressure upon inhalation of nitric oxide. (Applicants again remind the Examiner that systemic hypotension is not pulmonary edema, and has nothing whatsoever to do with pulmonary edema.) By the time INOmax® was approved for marketing in December 1999, those of ordinary skill in the art at the priority date were aware that inhaled nitric oxide will precipitate systemic hypotension in newborns who, like Henrichsen et al.'s patient, are diagnosed as dependent on a right-to-left shunt, and understood this to happen by a mechanism essentially as postulated by Henrichsen et al., i.e., by interfering with the right-to-left shunt on which the systemic circulation

depended. It could well be that the authors of Beghetti et al. were not aware of this fact when they wrote their letter in 1997 theorizing about another possible physiological mechanism to explain the observed systemic hypotension. At any rate, they do not propose that the patient in fact suffered an episode of pulmonary edema rather than the reported systemic hypotension. One of ordinary skill in the art at the priority date would read the Henrichsen et al. case study as being a typical example of the systemic hypotension that happens when a neonate who is dependent on a right-to-left shunt is treated with inhaled nitric oxide, and would read the Beghetti et al. letter as mere second-hand speculation inconsistent not only with Henrichsen et al.'s first-hand report about the shunt-reliant nature of the baby's circulation, but also with what was learned in subsequent years about such patients. ***More to the point, even Beghetti et al. does not propose that the baby was ever at any risk of pulmonary edema due to the treatment.*** Rather, Beghetti et al. merely sought to "explain the observed hypotensive effect of iNO". Thus, Beghetti et al.'s caution regarding "LV overfilling" on which the January 31, 2012 Office Action focuses (a) is based on unsubstantiated speculation about what was happening in the case report of Henrichsen et al. (speculation that is inconsistent with Henrichsen et al.'s first-hand diagnosis of dependence on a right-to-left shunt); and (b) purports to relate to a risk of systemic hypotension, not its conceptual opposite, pulmonary edema. One of ordinary skill would not derive from the Beghetti et al. letter any information of relevance to the present claims. It is not clear why the Examiner places any reliance at all on Beghetti et al.'s unsubstantiated speculation about a patient the authors never saw, in preference to Henrichsen et al.'s first-hand observations that are more consistent with accepted wisdom in the art, and even less clear why the Examiner believes a discussion of a patient who suffered systemic hypotension has anything to do with predicting a risk of pulmonary edema.

Ichinose et al.

> Ichinose et al. is briefly discussed on page 11 of the January 31, 2012 Office Action:
>
> Ichinose et al. teach inhalation of NO can increase left ventricle filling pressure in patients with severe left ventricle dysfunction and that it is important to be aware of the possibility that inhaled NO can produce pulmonary vasodilation and may overwhelm a failing left ventricle thereby producing **pulmonary edema** (page 3109 bottom left to top right columns). (Emphasis in the original)

Ichinose et al. is a review article entitled "Inhaled Nitric Oxide: A Selective Pulmonary Vasodilator: Current Uses and Therapeutic Potential." The January 31, 2012 Office Action focuses on one paragraph of the article, the paragraph spanning the left and right columns of page 3109. The paragraph begins with the sentence: "Inhaled NO has been demonstrated to be a selective pulmonary vasodilator in heart failure patients, although breathing NO was often accompanied by an elevation in LV filling pressure in patients with severe LV dysfunction," citing two publications, Semigram et al.[8] and Loh et al.[9] Both Semigram et al. and Loh et al. studied only adult patients suffering from severe heart failure. Thus, the quoted sentence from Ichinose et al. derives from observations made in adults with LVD associated with severe heart failure. Ichinose et al. goes on to say, "Investigators learned that the elevation in LV filling pressure that occurs with NO breathing is due to the augmentation of filling into a relatively noncompliant LV and is not caused by a negative inotropic effect," citing two more publications that again concern only adult conditions: Dickstein et al.[10] and Hare et al.[11] The statement of Ichinose et al. on which the January 31, 2012 Office Action relies ("Nonetheless, it is important to be aware of the possibility that inhaled NO can produce pulmonary vasodilation and may overwhelm a failing LV, thereby producing pulmonary edema.") cites only the Beghetti et al. letter, a reference that (as discussed above) says nothing about pulmonary edema and in fact is about a (neonatal) patient who, when treated with inhaled nitric oxide, exhibited systemic hypotension, a condition that is nothing like pulmonary edema. Beghetti et al. hypothesized that inhaled NO induced "further LV failure," i.e., caused the left ventricle to lose even more of its pumping capacity, offering this as an explanation for the drop in systemic blood pressure exhibited by the patient. It does not even begin to support an assertion that pulmonary edema

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[8] Semigram et al., J Am Coll Cardiol 24:982-988, 1994 (abstract cited in the January 31, 2012 Office action on page 19; full article enclosed with the Information Disclosure Statement filed April 20, 2012.

[9] This is the same Loh et al. as cited in the present rejection.

[10] Dickstein et al., J Heart Lung Transplant 15:715-721, 1996; cited in the Information Disclosure Statement filed April 20, 2012.

[11] Hare et al., Circulation 95:2250-2253, 1997; cited in the Information Disclosure Statement filed April 20, 2012.

could result in a pediatric patient. Thus, it appears doubtful that Ichinose et al. intended to imply, merely by citing Beghetti et al., that any patients other than adults might be at risk for pulmonary edema. This would have been a radical new assertion that would certainly have been discussed in detail with appropriate supporting evidence.

CONCLUSION

Applicants respectfully request that the above remarks, and the remarks and evidence (including objective evidence of nonobviousness) submitted in the 12/27/11 Reply, be taken into account by the Examiner when considering whether to re-assert the obviousness rejection in a new Office action. The January 31, 2012 Office action reveals a misunderstanding of many physiological facts described in the cited references and a possible misunderstanding of the overall effect of the limitations of the claims on claim scope, leading to a rejection based on inappropriate grounds. Applicants would be happy to meet with the Examiner again (together with SPE Kwon and QAS Burke, if they are available) at the Office's convenience if that would be helpful in clarifying the facts.

It is believed that no fees are due for this filing. If this is incorrect, please apply any necessary charges or credits to Deposit Account 06-1050, referencing the above attorney docket number.

Respectfully submitted,

Date: May 9, 2012

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EXHIBIT J

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	: James S. Baldassarre et al.	Art Unit	: 1613
Serial No.	: 12/821,041	Examiner	: Ernst V. Arnold
Filed	: June 22, 2010	Conf. No.	: 3219
Title	: METHODS OF REDUCING THE RISK OF OCCURRENCE OF PULMONARY EDEMA IN TERM OR NEAR-TERM NEONATES IN NEED OF TREATMENT WITH INHALED NITRIC OXIDE		

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

SUPPLEMENTAL AMENDMENT AND REMARKS

This application has been granted special status under the prioritized examination (Track 1) program. An Office action was mailed February 10, 2012, setting a three-month deadline for response of May 10, 2012. As indicated in the Interview Summary mailed by the Office on May 3, 2012, the Examiner informed the undersigned in a telephone call on April 23, 2012, that the Office action would be replaced with a new Office action. In addition, the transaction history for this application on PAIR has an entry dated April 24, 2012, that says "Withdrawing/Vacating Office Action Letter," and a second entry dated May 3, 2012, that says "Mail Notice of Withdrawn Action." Applicants thus assume that there is no longer a pending deadline for response, and there will be no deadline for response until the new Office action is mailed and thereby resets a new deadline.

Applicants ask that the present amendment be entered, and the below remarks considered, prior to preparation of a new Office action in this case.

Amendments to the Claims

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

Listing of Claims:

1-37. (Canceled)

38. (Currently amended) A method of reducing the risk of occurrence of pulmonary edema associated with a medical treatment comprising inhalation of nitric oxide gas, said method comprising:

(a) performing echocardiography to identify~~identifying~~ a term or near-term neonate patient in need of inhaled nitric oxide treatment for pulmonary hypertension, wherein the patient is not ~~known to be~~ dependent on right-to-left shunting of blood;

(b) determining that the patient identified in (a) has ~~pre-existing~~ left ventricular dysfunction and so is at particular risk of pulmonary edema upon treatment with inhaled nitric oxide; and

(c) excluding the patient from inhaled nitric oxide treatment based on the determination that the patient has ~~pre-existing~~ left ventricular dysfunction and so is at particular risk of pulmonary edema upon treatment with inhaled nitric oxide.

39. (Currently amended) The method of claim 38, wherein step (b) comprises performing echocardiography~~the patient has pulmonary hypertension~~.

40. (Currently amended) The method of claim 38, wherein step (b) comprises measuring the patient's pulmonary capillary wedge pressure~~ the patient has a pulmonary capillary wedge pressure that is greater than or equal to 20 mm Hg~~.

41. (Currently amended) A method of reducing the risk of occurrence of pulmonary edema associated with a medical treatment comprising inhalation of nitric oxide gas, said method comprising:

(a) ~~identifying a term or near-term neonate patient~~carrying out a diagnostic process comprising measuring blood oxygen level, to identify a term or near-term neonate patient as being in need of inhaled nitric oxide treatment for hypoxic respiratory failure, wherein the patient is not ~~known to be~~ dependent on right-to-left shunting of blood;

(b) performing echocardiography and/or measuring pulmonary capillary wedge pressure to determine that the patient has ~~determining by diagnostic screening that the patient identified in (a) has pre-existing~~ left ventricular dysfunction and so is at particular risk of pulmonary edema upon treatment with inhaled nitric oxide; and

(c) excluding the patient from treatment with inhaled nitric oxide based on the determination that the patient has ~~pre-existing~~ left ventricular dysfunction and so is at particular risk of pulmonary edema upon treatment with inhaled nitric oxide.

42. (Currently amended) The method of claim 41, wherein the diagnostic process of step (a) further comprises performing~~screening comprises~~ echocardiography.

43. (Currently amended) The method of claim 41, wherein step (b) comprises performing echocardiography~~the patient has pulmonary hypertension~~.

44. (Currently amended) The method of claim 41, wherein in step (b), the patient's pulmonary capillary wedge pressure is measured and determined to be ~~the patient has a pulmonary capillary wedge pressure that is~~ greater than or equal to 20 mm Hg.

45. (Currently amended) A method of treatment ~~reducing the risk of occurrence of pulmonary edema associated with medical treatment comprising inhalation of nitric oxide gas, said method~~ comprising:

(a) performing echocardiography to identify~~identifying~~ a plurality of term or near-term neonate patients who are in need of inhaled nitric oxide treatment for pulmonary

hypertension, wherein the patients are not ~~known to be~~ dependent on right-to-left shunting of blood;

(b) determining that a first patient of the plurality has ~~pre-existing~~ left ventricular dysfunction, so is at particular risk of pulmonary edema upon treatment with inhaled nitric oxide;

(c) determining that a second patient of the plurality does not have ~~pre-existing~~ left ventricular dysfunction;

(d) administering the 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 ~~pre-existing~~ left ventricular dysfunction, so is at particular risk of pulmonary edema upon treatment with inhaled nitric oxide.

46. (Currently amended) The method of claim 45, wherein step (a) further comprises measuring blood oxygen levels in the first and second patient and thereby determining that the first and second patient are hypoxic ~~have pulmonary hypertension~~.

47. (Previously presented) The method of claim 45, wherein the second patient has congenital heart disease.

48. (Currently amended) The method of claim 45, wherein step (b) comprises measuring the first patient's ~~the first patient has a~~ pulmonary capillary wedge pressure ~~greater than or equal to 20 mm Hg~~.

49. (Currently amended) The method of claim 45, wherein determining that the first patient of the plurality has pre-existing left ventricular dysfunction and the second patient of the plurality does not have pre-existing left ventricular dysfunction comprises performing echocardiography~~diagnostic screening~~.

50 - 52. (Canceled)

53. (New) A method of treatment comprising:

(a) identifying a plurality of term or near-term neonate patients who are in need of 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, performing echocardiography and/or measurement of pulmonary capillary wedge pressure to determine that the first patient of the plurality 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 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.

54. (New) The method of claim 53, wherein step (a) comprises performing echocardiography to determine that the first and second patients have pulmonary hypertension.

55. (New) The method of claim 53, wherein step (a) comprises measuring blood oxygen levels in the first and second patients and thereby determining that the first and second patients are hypoxic.

56. (New) The method of claim 53, wherein the second patient has congenital heart disease.

57. (New) The method of claim 53, wherein step (b) comprises measuring the first patient's pulmonary capillary wedge pressure and determining that it is greater than or equal to 20 mm Hg.

58. (New) The method of claim 38, wherein the patient's left ventricular dysfunction is attributable to congenital heart disease.

59. (New) The method of claim 38, wherein the patient is determined to be at particular risk not only of pulmonary edema, but also of other Serious Adverse Events, upon treatment with inhaled nitric oxide, and the patient is excluded from inhaled nitric oxide treatment based on the determination that the patient has left ventricular dysfunction and so is at particular risk not only of pulmonary edema, but also of other Serious Adverse Events, upon treatment with inhaled nitric oxide.

60. (New) The method of claim 41, wherein the left ventricular dysfunction is attributable to congenital heart disease.

61. (New) The method of claim 45, wherein the left ventricular dysfunction is attributable to congenital heart disease.

62. (New) The method of claim 46, wherein the left ventricular dysfunction is attributable to congenital heart disease.

63. (New) The method of claim 34, wherein the patient is determined to be at particular risk not only of pulmonary edema, but also of other Serious Adverse Events, upon treatment with inhaled nitric oxide, and the patient is excluded from inhaled nitric oxide treatment based on the determination that the patient has left ventricular dysfunction and so is at particular risk not only of pulmonary edema, but also other Serious Adverse Events, upon treatment with inhaled nitric oxide.

64. (New) The method of claim 63, wherein the left ventricular dysfunction is attributable to congenital heart disease.

65. (New) The method of claim 45, wherein the left ventricular dysfunction of the first patient is attributable to congenital heart disease.

66. (New) The method of claim 45, wherein the first patient is determined to be at particular risk not only of pulmonary edema, but also of other Serious Adverse Events, upon treatment with inhaled nitric oxide, and the first patient is excluded from inhaled nitric oxide treatment based on the determination that the first patient has left ventricular dysfunction and so is at particular risk not only of pulmonary edema, but also other Serious Adverse Events, upon treatment with inhaled nitric oxide.

67. (New) The method of claim 66, wherein the left ventricular dysfunction of the first patient is attributable to congenital heart disease.

68. (New) The method of claim 53, wherein the left ventricular dysfunction of the first patient is attributable to congenital heart disease.

69. (New) The method of claim 53, wherein the first patient is determined to be at particular risk not only of pulmonary edema, but also of other Serious Adverse Events, upon treatment with inhaled nitric oxide, and the first patient is excluded from inhaled nitric oxide treatment based on the determination that the first patient has pre-existing left ventricular dysfunction and so is at particular risk not only of pulmonary edema, but also other Serious Adverse Events, upon treatment with inhaled nitric oxide.

70. (New) The method of claim 69, wherein the left ventricular dysfunction of the first patient is attributable to congenital heart disease.

REMARKS

Upon entry of the above amendment, claims 38-49 and 53-70 will be pending, claims 50-52 having been newly canceled and new claims 53-70 added. Claims 1-37 were canceled in a prior amendment. Support for the amended and new claims can be found throughout the specification, e.g., in paragraphs [0004]-[0006], [0014], [0017], [0018], [0023], [0027]-[0029], [0033], [0039], [0040], and [0042]. No new matter has been added.

As there are only four independent claims and 30 total claims (and no multiply dependent claims) in the application following entry of the above amendment, this application continues to qualify for special status under the provisions for Prioritized Examination (Track 1).

Statement of the Substance of Multiple Telephonic Interviews

On April 23, 2012, Examiner Arnold telephoned the undersigned to confirm that the Office action mailed February 10, 2012 (the 2/10/12 Office action) was being withdrawn and would be replaced with a new Office action setting a new deadline for response.

On April 30, 2012, the undersigned spoke by telephone with SPE Brian Kwon, who noted that the Office actions in both the present case and a sister case (USSN 12/821,020) had been withdrawn and would be replaced with new Office actions.

Also on April 30, 2012, the undersigned spoke by telephone with SPE Marjorie Moran. SPE Moran confirmed that she had advised Examiner Arnold regarding how to apply the US Supreme Court's decisions concerning patent-eligible subject matter. SPE Moran provided some helpful, specific guidance for applicants as to what kinds of amendments might be useful in overcoming a potential rejection for lack of patent-eligible subject matter. Applicants are grateful for the guidance, and have closely followed SPE Moran's advice in drafting the present amendments.

Comments Regarding Some of the Present Amendments

The amendment deletes the term "pre-existing" from the phrase "pre-existing left ventricular dysfunction," wherever that phrase appears in the claims.

The amendment deletes the term "known to be" from the phrase "the patient is not known to be dependent on right-to-left shunting of blood," wherever that phrase appears in the claims.

The amendment adds at least one action step (e.g., "performing echocardiography") to each independent claim, as suggested by SPE Moran, in an effort to obviate any possible grounds for rejection for lack of patent-eligible subject matter under 35 USC § 101, and thereby expedite prosecution.

Request for Panel Decision

Applicants respectfully request that SPE Brian Kwon and QAS Julie Burke participate actively in the prosecution of this application as a panel with Examiner Arnold, as they are doing in a sister application, US application No. 12/821,020 (the '020 case). Applicants gratefully note that their perspective on the latter case has been very helpful to date in moving that case forward, and expect that it will similarly be helpful in the present case.

Discussion of technical points

The remarks below are intended to assist the Examiner in understanding some technical points that appear to applicants to be a source of confusion in this case and the '020 case. The topics covered are:

(1) the significance of the claim language "wherein the patient is not dependent on right-to-left shunting of blood";

(2) the description of the patient who is the subject of the claimed method;

(3) the disclosures of the various references cited in the obviousness rejection set forth in the 2/10/12 Office action; and

(4) the Examiner's conclusion that the art teaches that administering inhaled NO to babies with left ventricular dysfunction can cause pulmonary edema.

By resolving the apparent confusion regarding those four topics, applicants believe that these remarks should be very useful in moving the case forward efficiently.

(1) The significance of the claim language "*wherein the patient is not dependent on right-to-left shunting of blood.*"

The language "wherein the patient is not dependent on right-to-left shunting of blood" (or its equivalent "wherein the patients are not dependent on right-to-left shunting of blood") appears in step (a) of each of the pending independent claims, as amended above. It effectively narrows the scope of the claimed method by excluding outright some patients from the set of patients who are the subject of the method.

The term "dependent on right-to-left shunting of blood" is well understood in the medical art. See, for example, the use of this term in the 2007 INOmax® prescribing information[1] cited in the 2/10/12 Office action as the "INOmax insert" (page 2, left column, under "Contraindications"). The INOmax insert refers to a condition occasionally seen in neonates born with an absent or nonfunctional left ventricle -- the ventricle that normally pumps blood into the systemic circulation. Ordinarily, a neonate with an absent or nonfunctional left ventricle will die immediately from a lack of systemic circulation. Under certain circumstances, however, these neonates may survive: i.e., when two other independent conditions both happen to exist concurrently with the nonfunctional left ventricle: (i) an open (patent) ductus arteriosus, and (ii) an abnormally high level of pulmonary vascular resistance (routinely arising from pulmonary hypertension). When both of these conditions exist concurrently in a neonate who lacks a functional left ventricle, the neonate's right ventricle (which normally pumps blood only into the lungs) can take over the left ventricle's normal function of supplying blood flow to the systemic circulation. The right ventricle would have no outlet into the systemic circulation unless the infant's ductus arteriosus, a vascular connection between the pulmonary artery (which exits the right ventricle) and the aorta (which feeds the systemic circulation), remains open after birth. The ductus arteriosus normally closes at birth. If instead it remains open in a neonate who has

[1] Also commonly referred to as the "package insert" or "PI".

no functioning left ventricle, the ductus arteriosus will provide a conduit for some of the blood pumped by the right ventricle to shunt into the systemic circulation rather than taking its normal route into the lungs. This is termed a right-to-left shunt through a patent ductus arteriosus (PDA). If the neonate concurrently has pulmonary hypertension, this means relatively less blood goes from the right ventricle into the vasoconstricted lungs, thereby allowing more blood to shunt from the right ventricle through the PDA. In some cases, enough blood shunts through the PDA to sustain the systemic circulation. If the amount of blood flowing from the right ventricle through the PDA into the systemic circulation is sufficient to maintain life, and if the neonate's left ventricle is so severely dysfunctional that, absent this shunt through the PDA, the neonate would die from an inadequate systemic circulation, the neonate is said to be "***dependent*** on right-to-left shunting of blood." The reason this dependence on right-to-left shunting of blood has always been a contraindication on the INOmax® package insert since the product was first marketed is because it was known in the art that a patient who has pulmonary hypertension and is dependent on right-to-left shunting of blood, and who is treated with inhaled nitric oxide to open up the pulmonary blood vessels and thereby allow more blood to flow through the lungs, can suffer a catastrophic loss of the right-to-left blood flow through the PDA on which the patient depends for life.

There are many other situations in which a patient who is a candidate for treatment with inhaled nitric oxide (e.g., because the patient has pulmonary hypertension) exhibits a right-to-left shunt, a left-to-right shunt, or even a bi-directional shunt. Such a shunt can be through a PDA; through an open foramen ovale (a hole in the septum (wall) between the right and left atria); or through a hole in the septum between the left and right ventricles, termed a ventricular-septal defect. Except for the single situation described above with the particular combination of three conditions specified above (i.e., nonfunctional left ventricle, pulmonary hypertension, and a PDA through which blood shunts right-to-left in a volume that is sufficient to maintain the systemic circulation despite the nonfunctional left ventricle), the patient is not "dependent" on any of these shunts—i.e., his/her life does not depend on maintaining the shunt. In fact, it is more common that a shunt is harmful rather than helpful to the patient, because it diverts blood away

from its normal path through the right side of the heart to the lungs (where it is oxygenated), then into the left side of the heart, and from there into the systemic circulation for delivery to all parts of the body. For example, a right-to-left shunt at the atrial level, i.e., through the foramen ovale, means some of the deoxygenated blood entering the right atrium is shunted into the left atrium instead of taking its normal path into the right ventricle and then into the lungs. In such a patient, the "shunted" deoxygenated blood then passes from the left atrium into the left ventricle and is pumped by the left ventricle into the systemic circulation, still in its deoxygenated state, leaving the infant chronically poorly oxygenated. Far from being "dependent" on this right-to-left-shunt through the foramen ovale, the patient would be much better off without it.

The articles cited by the Examiner in the obviousness rejection described in the 2/10/12 Office action discuss in various contexts right-to-left shunts and left-to-right shunts (sometimes referring to the shunt as "exclusively" right-to-left or "exclusively" left-to-right). These shunts may occur at an open foramen ovale, or at a PDA, or at a ventricular-septal defect. The sole situation in which the patient is "dependent" on a shunt is the one described above, where the patient has a combination of *pulmonary hypertension, a severely dysfunctional or absent left ventricle, and a right-to-left shunt through a PDA that permits the right ventricle's output to reach the systemic circulation through the shunt.* (As described on page 452, left column, of Atz & Wessel, Seminars in Perinatology 1997, 21(5): 441-455 (one of the references cited in the 2/10/12 Office action), such a patient may also have, in addition to that combination of conditions, a left-to-right shunt through an open foramen ovale; such a patient is still characterized as "dependent on a right-to-left shunt" because of the critical role played by the right-to-left shunt through the PDA.) Characterizing a shunt as "exclusively" right-to-left or "exclusively" left-to-right means that the blood flows only in the indicated direction through that shunt. It does not mean, and does not even imply, that the patient is "dependent" on the shunt. In fact, most patients who have a shunt that is exclusively in one direction are harmed by the shunt--far from being "dependent" on it.

Applicants hope that the above discussion helps to clarify the significance of the word "dependent" in the claim language "dependent on right-to-left shunting of blood."

(2) The description of the patient who is the subject of the claimed method.

During an in-person interview with Examiner Arnold, SPE Kwon, and QAS Burke in the '020 application on April 13, 2012 (hereinafter the "4/13/12 Interview"), QAS Burke mentioned that the negative limitations of claim 31 of that application made the claim somewhat difficult to parse. Claim 31 of that application is highly similar to claim 38 of the present application, differing only in that the former refers to "child" while the latter refers to "term or near-term neonate patient." Applicants have attempted to simplify the claims of both cases by omitting the words "known to be" in step (a) of each independent claim.

Claim 38 as presently amended is a drawn to a method of reducing the risk of occurrence of pulmonary edema associated with a medical treatment comprising inhalation of nitric oxide gas, where the method includes identifying a narrowly defined category of term or near-term neonate patients who are in need of nitric oxide treatment but who are at particular risk of pulmonary edema from that treatment, and excluding from the treatment any patient who falls into that defined category of at-risk patients. It is important to note that the prior art was unaware that any neonates were at particular risk of pulmonary edema when treated with inhaled nitric oxide. The prior art did know that some neonates (i.e., those who are dependent on right-to-left shunting of blood) were at risk of systemic hypotension when treated with inhaled nitric oxide, but this risk has nothing to do with a risk of pulmonary edema and does not predict a risk of pulmonary edema. *Thus, the claim would be novel and nonobvious regardless of how the category of neonate patients to be excluded from the treatment is defined in the claim.* Since the basis for the invention was the discovery that children (including neonates) who have left ventricular dysfunction are surprisingly at risk for pulmonary edema when they are treated with inhaled nitric oxide, the claims include a limitation that the neonate to be excluded from treatment due to this risk is determined to have left ventricular dysfunction. In addition to this limitation on the scope of the claim, applicants have chosen to narrow the scope even further by explicitly requiring that the category of neonates covered by the claim not include those who are dependent on right to left shunting of blood.

Applicants hope that this discussion of the claims will help the Examiner understand the nature of the claims and the effect of the various limitations on claim scope.

(3) The disclosures of the various references cited in the obviousness rejection set forth in the 2/10/12 Office action.

The comments below address the following six references that were cited by the Office in support of the obviousness rejection in the 2/10/12 Office action. The below comments focus on what applicants believe are misinterpretations of the references expressed in that Office action. Applicants realize that Office action has been withdrawn and so the prior obviousness rejection is presently moot, but are concerned that the same references may be cited in a new Office action. Thus, to facilitate efficient prosecution, applicants would like to clarify for the Examiner's benefit what those references actually say regarding the points raised in the Office action. The references considered below are:

Fraisse et al., Cardiol Young 2004; 14:277-283;

Atz & Wessel (mentioned above);

Kinsella et al., The Lancet 1999; 354:1061-1065;

Loh et al., Circulation 1994; 90:2780-2785;

Beghetti et al., J. Pediatrics 1997; page 844;

Henrichsen et al., Journal of Pediatrics 1996; 129(1):183; and

Ichinose et al., Circulation 2004; 109:3106-3111.

Fraisse et al.

Applicants first point out that the senior author on Fraisse et al. is David L. Wessel, M.D. Dr. Wessel is also the senior author of Atz & Wessel. His views about the nonobviousness of the present invention are set forth in the Declaration of David L. Wessel, M.D. under 37 CFR § 1.132 submitted with applicants' Reply filed January 6, 2012 (the 1/6/12 Reply), and are discussed in detail in the 1/6/12 Reply. In brief, Dr. Wessel, who was presumably fully aware of both of these articles that he co-authored, says that he did not expect that children who have

pulmonary hypertension and LVD would be at increased risk of pulmonary edema upon inhalation of nitric oxide, until after the INOT22 clinical trial had proven, to his surprise, that this was indeed a real risk. That trial concluded long after Fraisse et al.'s 2004 publication date and Atz & Wessel's 1997 publication date. *This is a substantial clue that the Examiner's interpretation of these two articles as disclosing such a risk is incorrect.* That the Examiner's interpretation is indeed incorrect is borne out by a careful parsing of what Fraisse et al. and Atz & Wessel actually say. Applicants attempted to do that with respect to Atz & Wessel in the 1/6/12 Reply, and with respect to Fraisse et al. in the 4/13/12 Interview. Fraisse et al. is addressed in more detail here.

Fraisse et al. performed a retrospective analysis of echocardiographic features of newborns with persistent pulmonary hypertension who had been randomized to receive inhaled nitric oxide or other therapy in a previous clinical trial. The purpose of the Fraisse et al. analysis was to see whether these features could be used as a predictor of what the clinical trial had defined as a successful response to inhaled nitric oxide therapy. *See*, abstract. The clinical trial had defined a successful response to inhaled nitric oxide therapy as occurring when the patient survived without having to be placed on an alternative therapy (extracorporeal membrane oxygenation, "ECMO") to improve oxygenation. Fraisse et al. says nothing about pulmonary edema nor any other adverse events attributable to treatment with inhaled nitric oxide, except for noting that one patient whose systemic circulation was dependent on a right-to-left shunt through an open ductus arteriosus[2] experienced "haemodynamic deterioration" when inhaling nitric oxide

[2] The patient also reportedly had "an exclusively left-to-right shunt at the atrial level." In other words, the foramen ovale was open and allowed blood to flow in one direction, from the left atrium into the right atrium (i.e., left to right). In a patient who is dependent on a right-to-left shunt through a PDA, a left-to-right shunt through the foramen ovale has two effects: (1) it provides an outlet out of the left atrium for blood entering the left atrium from the lungs, thereby relieving pressure on the dysfunctional left ventricle; and (2) it allows oxygenated blood from the left atrium to mix with the deoxygenated blood being pumped from the right atrium into the right ventricle, which can pump it through the ductus arteriosus into the systemic circulation—i.e., it increases the oxygenation level of the blood entering the systemic circulation through the PDA.

(see page 281, upper left column). That haemodynamic deterioration was likely systemic hypotension,[3] i.e., not related to pulmonary edema.

> The 2/10/12 Office action at pages 4-5 characterizes Fraisse et al. in part as follows:
>
> Fraisse et al. teach that ***a left to right shunting of blood*** increases the risk of failing to respond to iNO including a patient with severe left ventricular dysfunction (Abstract and page 281 upper left column). (Emphasis in the original.)

The Fraisse et al. abstract and page 281, upper left column, does teach that left to right shunting of blood at the atrial level (i.e., through an open foramen ovale)[4] increased the risk of *failing to respond* to inhaled nitric oxide. Further, the cited part of Fraisse et al. at page 281, upper left column, does describe a patient with left to right shunting of blood at the atrial level who also had severe left ventricular dysfunction and who *failed to respond* to inhaled nitric oxide. However, the significance of those observations to the present claims is not clear, since the claims are not about identifying patients who will respond, or fail to respond, to inhaled nitric oxide. Rather, the claims are about reducing the risk of pulmonary edema. Pulmonary edema is a side effect that would be triggered by treatment with inhaled nitric oxide only when a patient's pulmonary hypertension responds well to the treatment—i.e., when the treatment is effective in relaxing the constricted pulmonary blood vessels, permitting an increased volume of blood to flow through the lungs and into the left side of the heart. It appears that the Examiner may have confused the concept of *failure to respond* to a given treatment with the concept of *adverse events* caused by the treatment. As noted by Dr. Greene during the 4/13/12 Interview, these are two entirely different concepts.

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[3] Elsewhere (page 280, top of right column) Fraisse et al. uses the term "haemodynamic instability" to mean "hypotension."

[4] A shunt at the "atrial level" is a shunt through the foramen ovale, a hole between the left atrium and right atrium (chambers of the heart). The word "atrial" should not be confused with the similar word "arterial", which refers to arteries and not chambers of the heart.

The Office action continues:

> Thus the patient is not known to be dependent on right to left shunting of blood and the patient had pre-existing left ventricular dysfunction before administration of iNO was performed.

The individual patient to which this sentence refers cannot be characterized, as the Office does, as "not known to be dependent on right to left shunting of blood." In fact, the description of that particular patient at page 281, upper left column, of Fraisse et al. says essentially the opposite:

> This last patient [who presented with persistent pulmonary hypertension], with an exclusively left-to-right shunt at the atrial level, also had a right-to-left ductal shunt. His left ventricular function was severely depressed, with echocardiographic evidence of a right ventricular dependent circulation. (Emphasis added)

A "right-to-left ductal shunt" is a right-to-left shunt through a patent ductus arteriosus (i.e., PDA). A "right ventricular dependent circulation" means, of course, that the right ventricle had taken over the job of supplying blood to the systemic circulation since the left ventricle's function was severely depressed. Fraisse et al. thus describes this neonatal patient as showing evidence of a combination of five conditions:

(i) persistent pulmonary hypertension;

(ii) an exclusively left-to-right shunt at the atrial level (i.e., through an open foramen ovale);

(iii) a right-to-left ductal shunt (i.e., through a PDA);

(iv) severely depressed left ventricular function (i.e., left ventricular dysfunction, or LVD); and

(v) evidence of a right ventricular dependent circulation (i.e., since his left ventricle was not functioning properly, the only way this patient survived was because his right ventricle had taken over the job of pumping blood into the systemic circulation, and that occurred only because the ductus arteriosus was open and permitted blood to flow from the pulmonary artery through the PDA into the aorta). This patient appears to fit the classic description of a neonatal LVD patient whose systemic circulation is dependent on right-to-left shunting of blood through a PDA, and who therefore should not be given inhaled nitric oxide because of the risk of systemic circulatory collapse, i.e., systemic hypotension. (See, e.g., the description of such newborns provided on page 452 of Atz & Wessel, as described in detail in applicants' 2/10/12 Reply at pages 12-15.)

Indeed, Fraisse et al. describes this particular patient as having "responded poorly to inhalation of nitric oxide, with persistence of hypoxaemia and haemodynamic deterioration." The "haemodynamic deterioration" was likely systemic hypotension induced by diversion of blood into the lungs and away from the PDA upon which the patient's systemic circulation depended, severely reducing the flow of blood into the systemic circulation. Applicants therefore submit that the Examiner is mistaken in asserting that this patient "is not known to be dependent on right to left shunting of blood." That plainly is not the case.

The 2/10/12 Office action continues by pointing to Table 2 of Fraisse et al. as giving clinical data and hemodynamic characteristics of 44 neonates who started treatment with inhaled nitric oxide. See, the 2/10/12 Office action at page 5. No explanation is provided as to what, if anything, in this table is considered to be relevant to the claims. Applicants note that, according to Table 2, three of the patients treated with inhaled nitric oxide reportedly had "moderately or severely depressed" left ventricular function. The table categorizes one of these as a "responder" (i.e., inhaled nitric oxide was effective) and two as "non-responders" (i.e., inhaled nitric oxide was not effective). Five other patients who were classified as having "mildly depressed" left ventricular function all were "responders." The table does not report any adverse events (pulmonary edema or otherwise) caused by the treatment in any patients. It therefore seems irrelevant to the claims, except as a possible *teaching-away*.

The 2/10/12 Office action then quotes extensively from pages 281 and 282 of Fraisse et al., without comment except to say on page 7: "The Examiner interprets 'reduced left ventricular compliance' to be a dysfunction of the left ventricle such that compliance is reduced." Absent the Examiner's views of why the lengthy quoted text is relevant to the claims, applicants are uncertain how to respond. *Below is a brief summary of the text that the 2/10/12 Office action quoted from pages 281 and 282 of Fraisse et al., with applicants' comments.*

The text from page 281 of Fraisse et al. is quoted on page 5 of the 2/10/12 Office action. It begins with a general description of how echocardiography is used in evaluating newborns with persistent pulmonary hypertension. It then discusses the authors' findings regarding left

and right ventricular function in the patients included in the study, including an observation that some patients had significant depression of left ventricular function.

The text from page 282 appears on pages 6-7 of the Office action. It was extracted from a paragraph of Fraisse et al. that begins by noting that several studies have shown that inhaled nitric oxide is effective in improving oxygenation and reducing the need for ECMO in newborns with persistent pulmonary hypertension. The quoted paragraph then says that the results of the present study indicate that those newborns with an exclusively left-to-right shunt across the atrial septum (i.e., through an open foramen ovale) have an increased risk of failing to respond to nitric oxide. *(Note that the authors did not assess side effects of the treatment, but rather only response or failure to respond.)* Fraisse et al. discuss the phenomenon of left-to-right shunting across the atrial septum in the context of a predominantly left-to-right ductal shunt and normal biventricular function, saying that "[in] this subgroup of patients, systemic oxygenation is significantly less improved by inhalation of nitric oxide"—i.e., the treatment is not as effective as it is in other patients. (Note that this particular discussion in Fraisse et al. refers to patients with "normal biventricular function," meaning that their left and right ventricles both function normally, so there is plainly no LVD; furthermore, it is about effectiveness of the treatment, not adverse events caused by the treatment. It therefore appears to be irrelevant to the present claims.)

According to the authors, left to right shunting across the atrial septum may also occur in another context: a patient with decreased left ventricular compliance may have increased left atrial pressure, and this can produce "a resultant left-to-right shunt across the oval foramen." In other words, the increased pressure built up in the left atrium because the left ventricle has decreased compliance can cause blood to escape the left atrium through the open foramen ovale into the right atrium (i.e., left to right). In this situation, the open foramen ovale acts like a pressure relief valve for the left atrium. Note that there is no suggestion that, instead of escaping through the foramen ovale, the blood would back up into the pulmonary vessels and produce pulmonary edema; rather, the only disclosed result of the increased left atrial pressure is a left to right shunt of blood from the left atrium into the right atrium. This shunt would presumably

serve to relieve at least some of the left atrial pressure, leaving one of skill in the art with no reason to expect that pulmonary edema would develop. Thus, this part of Fraisse et al. also appears to *teach away* from the presently claimed methods—and certainly does not support the rejection.

The reference goes on to explain what might cause decreased left ventricular compliance in patients with persistent pulmonary hypertension of the newborn. The causes listed by Fraisse et al. include adverse interaction between the ventricles (i.e., the adjacent left and right ventricles don't interact in a normal way, typically due to an enlarged right ventricle that is filled with blood at abnormally high pressure as it works hard to push blood into the constricted lung blood vessels); a leftward shift of the ventricular septum (i.e., the septum or wall shared by both ventricles is pushed "leftward" into the left ventricle's space by the enlarged right ventricle); decreased left ventricular diastolic filling (there is an inadequate volume of blood flowing from the vasoconstricted lungs into the left side of the heart, and less room in the left ventricle because of interference by the right ventricle, adding up to decreased filling of the left ventricle); and left ventricular systolic (emptying) dysfunction due to decreased preload (i.e., the "preload," or pressure exerted on the left ventricle by the blood present in the left atrium, is decreased due to the decreased flow of blood from the lungs into the left atrium and/or due to an open foramen ovale that permits blood to leak out of the left atrium into the right atrium; this decreased preload can make the left ventricle less efficient at contracting), hypoxaemia (low oxygenation), and acidosis (increased acidity of the blood). Fraisse et al. then describe what happens when left ventricular systolic (emptying) function is severely depressed in newborns with persistent pulmonary hypertension: the right ventricle takes over, providing blood flow to the systemic circulation by pumping blood through the patent (open) arterial duct (i.e., the PDA). In other words, this patient's systemic circulation is dependent on the right-to-left shunt through the PDA. As taught by Fraisse et al. on page 282, top of right column, treating such a patient with inhaled nitric oxide "may not give the desired clinical response, because the blood flowing across the duct is redistributed away from the systemic circulation towards the lungs, decreasing post-ductal systemic output, and increasing the left atrial pressure." Thus, Fraisse et al. points

out that neonates whose systemic circulation is dependent on a right-to-left shunt through the open ductus are expected to suffer a loss of "post-ductal systemic output" (i.e., flow from the right side of the heart through the open ductus into the systemic circulation) if they are treated with inhaled nitric oxide—i.e., they may end up with life-threatening systemic hypotension. This is, of course, the well-known contraindication for inhaled nitric oxide in patients who are dependent on a right-to-left shunt, a set of patients explicitly outside the category of neonates defined in part (a) of each of the independent claims. This discussion by Fraisse et al. therefore has nothing to do with the category of patients to whom the claimed method applies. Furthermore, ***it has nothing to do with pulmonary edema.***

Applicants note for the record that Fraisse et al.'s reference to "increasing the left atrial pressure" as one of the effects of inhaled nitric oxide in these patients does not imply that pulmonary edema would result. For example: if, prior to the treatment, the left atrial pressure was below normal (as may occur when pulmonary hypertension has reduced the blood flow into the left atrium, and as confirmed by the reference in the quoted text to "decreased preload"[5]), the increase in left atrial pressure following the treatment may just bring the pressure up to a normal range. Thus, the observation about "increasing the left atrial pressure" does not in itself imply any pathology. Further, the cite provided by Fraisse et al. as support for the statement about "decreasing post-ductal systemic output, and increasing the left atrial pressure" is Henrichsen et al., *J. Pediatr.* 1996; 129:183, a case study of a single infant who was reported to be dependent on a right-to-left shunt and who suffered systemic hypotension (not pulmonary edema) after being treated with inhaled nitric oxide. Applicants submit that the sole relevance of this part of Fraisse et al. is as a description of patients who are dependent on a right-to-left shunt at the ductus arteriosus, a set of patients explicitly carved out of the category of neonates that is the subject of the claimed methods. ***Thus, Fraisse et al.'s teaching regarding what occurs in neonates dependent on right-to-left shunting of blood is entirely irrelevant to the claimed methods.***

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[5] Fifth line from the bottom of page 5 of the Office action. "Preload" in this context is the pressure exerted on the left ventricle by the volume of blood present in the left atrium. "Decreased preload" means the pressure is below normal.

The final passage that the 2/10/12 Office action quotes from Fraisse et al. is taken from the last paragraph on page 282. The sentence fragment "are at increased risk of death" that begins the quoted section is derived from a sentence that reads in full: "A pure right-to-left ductal shunt identified the patients who are at increased risk of death." This "risk of death" was not attributed to the treatment *per se*, but rather to the underlying condition. (*See*, e.g., page 281, right column, second full paragraph.) Further, Fraisse et al. does not suggest that the patients found to be at increased risk of death had LVD, nor that they suffered from pulmonary edema. That part of the quoted text is therefore, for several reasons, irrelevant to the present claims. The quoted section then says, "A pure left-to-right ductal shunt tends to be associated with greater need for extracorporeal membrane oxygenation, and should prompt cautious re-evaluation of the indication for further treatment aimed at increasing pulmonary vasodilation." Applicants cannot see how this statement is at all pertinent to the presently claimed methods. It does not suggest that the patients with the left-to-right ductal shunt had LVD, and it concerns the lack of efficacy of inhaled nitric oxide in patients with a left-to-right ductal shunt--not adverse events (pulmonary edema or anything else) attributable to this treatment. If the Examiner intends to cite Fraisse et al. (and these statements of Fraisse et al. in particular) in a new obviousness rejection, he is respectfully asked to clarify why he believes these statements of Fraisse et al. to be relevant. They appear to be as irrelevant as the other Fraisse et al. text discussed above.

In sum, Fraisse et al. is concerned with using echocardiography to identify neonates in whom inhaled nitric oxide is less likely to be efficacious—i.e., who died from their underlying condition despite the inhaled nitric oxide treatment, or who had to be put on ECMO in an effort to improve their oxygenation and keep them alive. Though some of the neonates in the trial analyzed by Fraisse et al. did have evidence of LVD, the authors do not link that observation to any identified risk—or even a reduction in efficacy--of the treatment, except for one patient in whom LVD was combined with dependence on a right-to-left shunt at the ductus arteriosus, so who is explicitly outside the population of patients defined as the subject of the present claims. In fact, the utter lack of any mention by Fraisse et al. of an actual or expected increased incidence of pulmonary edema in *any* subset of the neonates in the study following treatment

with inhaled nitric oxide suggests that no such increased incidence was expected, much less found. Further, Fraisse et al. observed that increased left atrial pressure due to decreased left ventricular compliance was associated with an escape valve of sorts: a flow of blood from the left atrium to the right atrium through the open oval foramen.[6] ***Thus, Fraisse et al.'s only apparent relevance to the present claims is as a teaching away.***

If the Examiner disagrees with this assessment of the Fraisse et al. article, he is asked to explain why.

Atz & Wessel

The alleged teachings of Atz & Wessel are described on pages 7-8 of the 2/10/12 Office action:

> Atz et al. warn that sudden pulmonary vasodilation may produce **pulmonary edema** (page 452, left column). Atz et al. teach that: "Caution should be exercised when administering NO to patients with severe left ventricular dysfunction and pulmonary hypertension." (page 452, left column).... Atz et al. continues with: "Therefore, in newborns with severe left ventricular dysfunction, predominantly left to right shunting at the foramen ovale and exclusively ***right to left shunting*** at the ductus arteriosus, ***NO should be used with extreme caution, if at all***. We and others have reported ***adverse outcomes*** in this circumstance." (page 452, left column) (Examiner added emphasis). Therefore it is known in the art that patients who had pre-existing LVD treated with NO for any duration may experience adverse outcomes.... Thus, Atz et al. fairly teaches excluding patients which include pediatric patients with left ventricular dysfunction from inhaled NO treatment because the Examiner interprets "if at all" to mean no treatment and hence exclusion from treatment. The left ventricular dysfunction is intrinsically pre-existing.
>
> To summarize, the methods disclosed by Atz et al. are interpreted to mean:
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> - identifying a patient eligible for NO treatment;
> - diagnosing/identifying if the patient has left ventricular dysfunction;
> - excluding that patient with left ventricular dysfunction from treatment with NO but treating the patient with NO for other conditions discussed by Atz et al. with inhalation of NO thereby reducing the risk of adverse events associated with the medical treatment.

[6] Page 282, left column, last paragraph.

This characterization of Atz & Wessel is exactly the same as the one presented on pages 9-10 of the Office action dated June 27, 2011 (the "6/27/11 Office action"). Applicants' reply to the 6/27/11 Office action (the 1/6/12 Reply) included a detailed rebuttal of the Examiner's characterization of Atz & Wessel, pointing out that the Examiner's interpretation of the Atz & Wessel reference was far broader than what it really says. See pages 10-18 of the 1/6/12 Reply. Applicants' arguments were not simply opinion, but rather were supported by a careful parsing of the crucial paragraph on page 452 of the reference as well as by factual evidence submitted with the 1/6/12 Reply, and were intended to assist the Examiner in coming to a clearer understanding what the reference actually communicated to those of skill in the art. Unfortunately, rather than address applicants' arguments and evidence about what this reference says, either agreeing with them or pointing out any perceived errors or deficiencies in applicants' submission so that applicants can respond, the 2/10/12 Office action simply repeats, word for word, the prior overbroad characterization of the reference, dismissing applicants' entire submission regarding Atz & Wessel as "moot." Applicants fail to see how guidance as to how to interpret a reference's disclosure can possibly be "moot" if the reference is still being cited for exactly the same alleged disclosure. Forcing applicants to re-present the same arguments and evidence already of record, to address exactly the same points addressed by applicants' prior remarks, does not advance prosecution in an efficient way, wasting time, money and the Office's resources, and delaying a resolution in this case. Applicants request that the Examiner provide a substantive response, either accepting applicants' positions or explaining why, in the Examiner's view, the facts do not support these positions.

Rather than re-submit the entire nine pages of arguments (and related exhibits) about the Atz & Wessel reference submitted in the 1/6/12 Reply, applicants direct the Examiner's attention to pages 10-18 of the 1/6/12 Reply and to Exhibits A-C submitted with that reply. In those nine pages, supported by Exhibits A-C, applicants explained that the broad statement at the beginning of the pertinent paragraph of Atz & Wessel must be read in the context of the rest of the paragraph, which explains that the entire universe of LVD patients at risk from treatment with

inhaled nitric oxide is limited to the two defined patient groups well known in the art to be at risk: adults with ischemic cardiomyopathy (who are at risk of pulmonary edema) and newborns who are dependent on a right-to-left shunting of blood (who are at risk of systemic circulatory collapse). Atz & Wessel did not suggest that inhaled nitric oxide treatment might pose a particular risk to any other patient group (whether with or without LVD), and certainly did not suggest that the treatment might trigger pulmonary edema in anyone but adults with LVD due to ischemic cardiomyopathy. The 2/10/12 Office action's purported summary of Atz & Wessel as implying that all patients (including all pediatric patients) with LVD should be excluded from treatment with inhaled nitric oxide is simply wrong. Further, the risk recited in the present claims is specified as being pulmonary edema, a risk that Atz & Wessel discussed solely in the context of adult patients—not the neonates specified in the claims. There was no recognition whatsoever in Atz & Wessel, or in any of the other cited art, that neonates or any other non-adult patients with LVD might be at risk of pulmonary edema upon treatment with inhaled nitric oxide. Dr. Wessel's declaration (Exhibit C submitted with the 1/6/12 Reply) establishes that in fact his Atz & Wessel article did not disclose that pediatric LVD patients--other than those dependent on a right-to-left shunt, who are known to be at risk of systemic hypotension, not pulmonary edema--were at any risk from the treatment, and that he was surprised when the new risk was discovered in the course of the INOT22 clinical trial that he helped design in 2006. As noted by Dr. Wessel, if he had expected children with LVD who are not dependent on a right-to-left shunt to be at risk from the treatment, he would not have allowed them to be included in the clinical trial. The Examiner is asked to give due consideration to the detailed explanation of Atz & Wessel provided on pages 10-18 of the 1/6/12 Reply, and to the factual evidence submitted in support thereof, and to acknowledge that the description of this reference provided in the last two Office actions does not accurate reflect what the reference discloses.

Kinsella et al.

As with the Atz & Wessel reference, the 2/10/12 Office action's characterization of Kinsella et al. at page 9 is word-for-word identical to the way Kinsella et al. was characterized in

the 6/27/11 Office action. Also as with the Atz & Wessel reference, applicants' discussion of Kinsella et al. at pages 18-21 of the 1/6/12 Reply, though entirely relevant to how this reference is described and cited in the present rejection, was dismissed as "moot" by the 2/10/12 Office action, rather than being addressed on the merits. Applicants ask the Examiner to give due consideration to the detailed discussion of Kinsella et al. provided at pages 18-21 of the 1/6/12 Reply, including the factual evidence (Exhibits C and D) cited in support of that discussion. In brief, that discussion establishes that one of ordinary skill in the art would have viewed Kinsella et al. as irrelevant to the present claims. It is noted that the Examiner has not even attempted to rebut applicants' position.

Loh et al.

At risk of sounding repetitive, applicants point out that the 2/10/12 Office action's characterization of yet another reference--Loh et al.--is again word-for-word identical to the way this reference was characterized in the 6/27/11 Office action. See pages 9-10 of the 2/10/12 Office action. As with applicants' discussion of Atz & Wessel and Kinsella et al., applicants' discussion of Loh et al. at pages 21-22 of the 1/6/12 Reply, though entirely relevant to how this reference is described and cited in the present rejection, was inappropriately dismissed as "moot" by the 2/10/12 Office action rather than being addressed on the merits. Applicants ask the Examiner to give due consideration to the detailed discussion of Loh et al. provided at pages 21-22 of the 1/6/12 Reply, including the fact that Loh et al. is solely about adult patients who have an importantly different form of LVD than that typically found in neonates. That is, the adult form of LVD that concerns Loh et al. (diastolic LVD) renders the left ventricle stiff and unable to stretch readily to accept blood, while childhood LVD is generally characterized by a weak, flabby left ventricle that stretches easily but has weak contractions.[7] These assertions are supported by factual evidence submitted with the

[7] The 2/10/12 Office action at page 7 points to page 282 of Fraisse et al. as evidence that children can have "reduced left ventricular compliance." Dr. Greene addressed this phenomenon in the 4/13/12 Interview. According to Dr. Greene, the "reduced left ventricular compliance" to which Fraisse et al. referred is a temporary situation attributable to the fact that the patient has pulmonary hypertension. Pulmonary hypertension means that the right ventricle has to work extra hard to push blood into the vasoconstricted lungs. The increased pressure in the right

1/6/12 Reply, evidence that has not yet been considered on the record by the Examiner. Applicants have explained in detail in the 1/6/12 Reply why one of ordinary skill in the art would not have expected the results in adults (as reported by Loh et al.) to be duplicated in children, citing factual evidence to support this position. The Examiner is asked to address applicants' position and evidence on the record, rather than again dismissing it as "moot."

Beghetti et al. and Henrichsen et al.

Beghetti et al. is a newly cited brief Letter to the Editor in the Journal of Pediatrics, written in response to a prior Letter to the Editor in the same journal entitled "Inhaled nitric oxide can cause severe systemic hypotension" (Henrichsen et al., J. Pediatrics 129:183,1996; listed as "pertinent to applicant's disclosure" on page 19 of the 2/10/12 Office action). In order to put Beghetti et al.'s comments into context, it is necessary to review what Henrichsen et al. said.

Henrichsen et al. is a case study of a newborn baby who was given inhaled nitric oxide as a treatment for persistent pulmonary hypertension. The baby is said to have had severe left ventricular dysfunction and a PDA, and was diagnosed as being "dependent on the right-to-left shunt through the PDA." Because of that dependence on right to left shunting of blood, the baby described by Henrichsen et al. (and discussed after-the-fact by Beghetti et al.) is not within the population of patients that is the subject of each of the independent claims, all of which specify that the subject patient(s) "is/are not dependent on right-to-left shunting of blood." Treatment of Henrichsen et al.'s patient with inhaled nitric oxide "resulted in an immediate fall in the mean systemic arterial blood pressure from 48 to 35 mmHg, which reversed when NO therapy was discontinued," i.e., the baby experienced systemic hypotension upon inhalation of NO. According to Henrichsen et al., "This hypotensive episode was thought to have been caused by

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ventricle expands the size of the right ventricle, which pushes against the left ventricle and reduces its "compliance"—i.e., its ability to fill. When such a patient is treated with inhaled nitric oxide to open up the constricted pulmonary blood vessels, blood flows out of the right ventricle into the lungs, thereby reducing the pressure and size of the right ventricle so that it no longer interferes with the left ventricle. The left ventricle then recovers its normal level of compliance and is able to handle the increased flow from the lungs. Thus, there would be no expectation that pulmonary edema might develop upon treatment of such a patient with inhaled nitric oxide.

the NO's reversing the right-to-left shunt through the PDA on which the systemic circulation depended." In other words, the baby's systemic circulation was dependent on a right-to-left shunt through a PDA and was adversely affected, resulting in hypotension, when inhaled nitric oxide reduced the patient's pulmonary hypertension. This of course is exactly what is now well known to occur in neonates who are dependent on right-to-left shunting of blood, and is why the INOmax insert said that such neonates are contraindicated for treatment with inhaled nitric oxide. Henrichsen et al. says nothing about inhaled nitric oxide's having caused any problems other than systemic hypotension. ***In particular, there is no mention of pulmonary edema.*** As discussed by Dr. Greene during the 4/13/12 Interview, pulmonary edema and systemic hypotension are entirely different and conceptually inconsistent conditions, one being treated by decreasing fluids and the other being treated by increasing fluids.

Beghetti et al. read the case study published by Henrichsen et al. and offered their own interpretation of what may have been occurring in the infant. They dismissed Henrichsen et al.'s view that the baby was dependent on a right-to-left shunt and suggested that the systemic hypotension exhibited upon treatment with inhaled nitric oxide was instead due to further left ventricular failure caused by "overfilling"—i.e., the left ventricle was even less able to pump than it was before the treatment began, thereby reducing the blood flow out of the left ventricle and contributing to systemic hypotension. Though Beghetti et al. appeared perfectly willing to speculate about what might have been occurring, despite not having seen the baby or any data other than that provided in Henrichsen et al.'s letter, ***they do not even suggest that the proposed "overfilling" of the left ventricle might have precipitated pulmonary edema in the baby***. Beghetti et al. simply offered an alternative explanation for the observed fall in systemic blood pressure upon inhalation of nitric oxide. (Applicants again remind the Examiner that systemic hypotension is not pulmonary edema, and has nothing whatsoever to do with pulmonary edema.) By the time the INOmax® product was approved for marketing in December 1999, those of ordinary skill in the art at the priority date were aware that inhaled nitric oxide will precipitate systemic hypotension in newborns who, like Henrichsen et al.'s patient, are diagnosed as dependent on a right-to-left shunt, and understood this to happen by a mechanism essentially as

postulated by Henrichsen et al., i.e., by interfering with the right-to-left shunt on which the systemic circulation depended. It could well be that the authors of Beghetti et al. were not aware of this fact when they wrote their letter in 1997 theorizing about another possible physiological mechanism to explain the observed systemic hypotension. At any rate, they do not propose that the patient in fact suffered an episode of pulmonary edema, rather than the reported systemic hypotension. One of ordinary skill in the art at the priority date would read the Henrichsen et al. case study as being a typical example of the systemic hypotension that happens when a neonate who is dependent on a right-to-left shunt is treated with inhaled nitric oxide, and would read the Beghetti et al. letter as mere second-hand speculation inconsistent not only with Henrichsen et al.'s first-hand report about the shunt-reliant nature of the baby's circulation, but also with what was learned in subsequent years about such patients. ***More to the point, even Beghetti et al. does not propose that the baby was ever at any risk of pulmonary edema due to the treatment.*** Rather, Beghetti et al. merely sought to "explain the observed hypotensive effect of iNO". Thus, Beghetti et al.'s caution regarding "LV overfilling" on which the 2/10/12 Office action focuses is based on unsubstantiated speculation about what was happening in the case report of Henrichsen et al. (speculation that is inconsistent with Henrichsen et al.'s first-hand diagnosis of dependence on a right-to-left shunt); and furthermore purports to relate to a risk of systemic hypotension, not its conceptual opposite, pulmonary edema. One of ordinary skill would not derive from the Beghetti et al. letter any information of relevance to the present claims. It is not clear why the Examiner places any reliance at all on Beghetti et al.'s unsubstantiated speculation about a patient the authors never saw, in preference to Henrichsen et al.'s first-hand observations that are more consistent with accepted wisdom in the art, and even less clear why the Examiner believes a discussion of a patient who suffered systemic hypotension has anything to do with predicting a risk of pulmonary edema.

Ichinose et al.

Ichinose et al. is briefly discussed on page 11 of the 2/10/12 Office action:

> Ichinose et al. teach inhalation of NO can increase left ventricle filling pressure in patients with severe left ventricle dysfunction and that it is important to be aware of the

> possibility that inhaled NO can produce pulmonary vasodilation and may overwhelm a failing left ventricle thereby producing **pulmonary edema** (page 3109 bottom left to top right columns). (Emphasis in the original)

Ichinose et al. is a review article entitled "Inhaled Nitric Oxide: A Selective Pulmonary Vasodilator: Current Uses and Therapeutic Potential." The 2/10/12 Office action focuses on one paragraph of the article, the paragraph spanning the left and right columns of page 3109. The paragraph begins with the sentence: "Inhaled NO has been demonstrated to be a selective pulmonary vasodilator in heart failure patients, although breathing NO was often accompanied by an elevation in LV filling pressure in patients with severe LV dysfunction," citing two publications, Semigram et al.[8] and Loh et al.[9] Both Semigram et al. and Loh et al. studied only adult patients suffering from severe heart failure. Thus, this quoted sentence from Ichinose et al. derives from observations made in adults with LVD associated with severe heart failure. Ichinose et al. goes on to say, "Investigators learned that the elevation in LV filling pressure that occurs with NO breathing is due to the augmentation of filling into a relatively noncompliant LV and is not caused by a negative inotropic effect," citing two more publications that again concern only adult conditions: Dickstein et al.[10] and Hare et al.[11] The statement of Ichinose et al. on which the 2/10/12 Office action relies ("Nonetheless, it is important to be aware of the possibility that inhaled NO can produce pulmonary vasodilation and may overwhelm a failing LV, thereby producing pulmonary edema") cites only the Beghetti et al. letter, a reference that (as discussed above) says nothing about pulmonary edema and in fact is about a (neonatal) patient who, when treated with inhaled nitric oxide, exhibited systemic hypotension, a condition that is nothing like pulmonary edema. Beghetti et al. hypothesized that inhaled NO induced "further LV failure," i.e., caused the dysfunctional left ventricle to lose even more of its pumping capacity, offering

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[8] Semigram et al., J Am Coll Cardiol 24:982-988, 1994 (cited in the 2/10/12 Office action on page 19 and in the Information Disclosure Statement filed June 22, 2010.

[9] This is the same Loh et al. as cited in the present rejection.

[10] Dickstein et al., J Heart Lung Transplant 15:715-721, 1996; cited in the Information Disclosure Statement filed April 23, 2012.

[11] Hare et al., Circulation 95:2250-2253, 1997; cited in the Information Disclosure Statement filed March 14, 2011.

this as an explanation for the drop in systemic blood pressure exhibited by the patient. It does not even begin to support an assertion that pulmonary edema could result in a neonate who is treated with inhaled nitric oxide. Thus, it appears doubtful that Ichinose et al. intended to imply, merely by citing Beghetti et al., that any patients other than adults might be at risk for pulmonary edema. This would have been a radical new assertion that would certainly have been discussed in detail with appropriate supporting evidence.

(4) The Examiner's conclusion that the art teaches that administering inhaled NO to babies with left ventricular dysfunction can cause pulmonary edema.

Pages 11-12 of the 2/10/12 Office action set out five rhetorical questions and the Examiner's view as to their answers. Since that Office action is being withdrawn and the points made by this part of the Office action may not be asserted in a new Office action, applicants will not belabor them here. However, applicants wish to note for the record that the Examiner's stated assumptions about what the "preponderance of art cited clearly indicates" and what the "art cautions and warns" are not supported by any of the references cited in the Office action. The only references to pulmonary edema in the cited art are in the context of adults, not neonates. All discussion in the art regarding risks to neonates in particular describe the risk as a risk of systemic hypotension, not pulmonary edema.

CONCLUSION

Applicants respectfully request that the above remarks, and the remarks and evidence (including objective evidence of nonobviousness) submitted in the 1/10/12 Reply, be taken into account by the Examiner when considering whether to assert an obviousness rejection (based on any of the above-discussed references or any others) in a new Office action. The 2/10/12 Office action reveals a misunderstanding of many physiological facts described in the cited references and a possible misunderstanding of the overall effect of the limitations of the claims on claim scope, leading to a rejection based on inappropriate grounds. Applicants would be happy to meet

with the Examiner again (together with SPE Kwon and QAS Burke, if they are available) at the Office's convenience, if that would be helpful in clarifying the facts.

The excess claims fee of $300 is being paid concurrently herewith. If any other fees are due, please apply them to deposit account 06-1050, referencing the above attorney docket number.

Respectfully submitted,

Date: May 11, 2012

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EXHIBIT K

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:

[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

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[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

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EXHIBIT L

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EXAMINER	
ARNOLD, ERNST V	
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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

EXHIBIT M

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE (USPTO)	
Application Serial Number	TBD
Confirmation Number	1376
Filing Date	Herein
Title of Application	Methods of Treating Term and Near-Term Neonates Having Hypoxic Respiratory Failure Associated with Clinical or Echocardiographic Evidence of Pulmonary Hypertension
First Named Inventor	James S. Baldassarre
Assignee	Ikaria, Inc.
Group Art Unit	1614
Examiner	TBD
Attorney Docket Number	I001-0002USC3

ACCELERATED EXAMINATION SUPPORT DOCUMENT

Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

Sir:

This Accelerated Examination Support Document (AESD) is submitted in support of the Petition for Accelerated Examination filed herewith.

Claims 1-20 are currently pending in the continuation application. A listing of the claims starts on page 2 herein.

The remaining sections of the AESD begin on page 6. Consideration and grant of the Petition to Accelerate Examination is respectfully requested.

CLAIMS

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

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

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

2. The method of claim 1, wherein the adverse event or serious adverse event is one or more of pulmonary edema, hypotension, cardiac arrest, electrocardiogram changes, hypoxemia, hypoxia and bradycardia, or, associations thereof.

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

4. The method of claim 3, wherein the left ventricular afterload is minimized or reduced by administering a pharmaceutical dosage form comprising nitroglycerin or calcium channel blocker to the patient.

5. The method of claim 3, wherein the left ventricular afterload is minimized or reduced using an intra-aortic balloon pump.

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

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

b. informing the medical provider that such patients that have pre-existing left ventricular dysfunction experience an increased rate of adverse events or serious adverse events associated with said medical treatment.

7. The method of claim 6, further comprising informing the medical provider of a risk of an adverse event or a serious adverse event in such patients who have a pulmonary capillary wedge pressure greater than 20 mm Hg.

8. The method of claim 6, further comprising informing the medical provider that there is a risk associated with using inhaled nitric oxides in such patients who have pre-existing or clinically significant left ventricular dysfunction and that such risk should be evaluated on a case by case basis.

9. The method of claim 6, further comprising informing the medical provider that there is a risk associated with using inhaled nitric oxide in such patients who have left ventricular dysfunction.

10. The method of claim 6, further comprising reducing left ventricular afterload to minimize or reduce the risk of the occurrence of an adverse event or serious adverse event being pulmonary edema in the patient.

11. The method of claim 10, wherein the left ventricular afterload is minimized or reduced by administering a pharmaceutical dosage form comprising nitroglycerin or calcium channel blocker to the patient.

12. The method of claim 10, wherein the left ventricular afterload is minimized or reduced using an intra-aortic balloon pump.

13. A method of reducing one or more adverse events or serious adverse events in an intended patient population comprising neonates or near-term neonates in need of being treated with inhaled nitric oxide comprising:

a. identifying a patient eligible for inhaled nitric oxide treatment;

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

c. excluding from inhaled nitric oxide treatment any patient having pre-existing left ventricular dysfunction.

14. The method of claim 13, wherein the patient having pre-existing left ventricular dysfunction also exhibits a pulmonary capillary wedge pressure greater than 20 mm Hg.

15. The method of claim 13, further comprising reducing left ventricular afterload to minimize or reduce the risk of the occurrence of an adverse event or serious adverse event being pulmonary edema in the patient.

16. The method of claim 15,

wherein the left ventricular afterload is minimized or reduced by administering a pharmaceutical dosage form comprising nitroglycerin or calcium channel blocker to the patient, or,

wherein the left ventricular afterload is minimized or reduced using an intra-aortic balloon pump.

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

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

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

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

18. The method of claim 17, wherein the patient diagnosed as having pre-existing left ventricular dysfunction also exhibits a pulmonary capillary wedge pressure greater than 20 mm Hg.

19. The method of claim 17, further comprising reducing left ventricular afterload to minimize or reduce the risk of the occurrence of an adverse event or serious adverse event being pulmonary edema in the patient.

20. The method of claim 19,

wherein the left ventricular afterload is minimized or reduced by administering a pharmaceutical dosage form comprising nitroglycerin or calcium channel blocker to the patient, or,

wherein the left ventricular afterload is minimized or reduced using an intra-aortic balloon pump.

9(A) References Deemed Most Closely Related

An Information Disclosure Statement in compliance with 37 CFR 1.98 has been filed herewith citing each of the following references deemed most closely related to the subject matter of the claims. The references listed in the IDS submitted herewith but not listed in this Petition are not closely related to the claimed invention particularly as compared to the references listed and discussed herein.

List of Most Closely Related References

Use of Nitric Oxide, American Academy of Pediatrics, Pediatrics, Vol. 106, No. 2, August 2000, pp. 344-345. ("AAP").

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Adatia I et al., Inhaled Nitric Oxide and Hemodynamic Evaluation of Patients With Pulmonary Hypertension Before Transplantation, JADD, Vol. 25, No. 7, June 1995, pp. 1656-64. ("Adatia").

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9(B) Identification of Limitations Disclosed by References

AAP:

In August 2000, the Committee on Fetus and Newborn of the American Academy of Pediatrics issued a report on the use of iNO in infants. A relevant portion states:

> iNO should be administered using FDA-approved devices that are capable of administering iNO in constant concentration ranges in parts per million or less throughout the respiratory cycle. Infants who receive iNO therapy should be monitored according to institutionally derived protocols designed to avoid the potential toxic effects associated with iNO administration. These effects include methemoglobinemia (secondary to excess nitric oxide concentrations), direct pulmonary injury (attributable to excess levels of nitrogen dioxide), and ambient air contamination.

(P. 344, 2nd col.). AAP also lists seven RECOMMENDATIONS. (Pp. 344-345). However, AAP is completely silent respecting excluding from iNO treatment any child patient diagnosed with pre-existing left ventricular dysfunction.

Lipshultz:

Lipshultz teaches that data or information gleaned from iNO studies in adults does not correlate or is otherwise probative of iNO studies in children. In other words, children with ventricular dysfunction must be diagnosed, understood, and treated differently than adult patients diagnosed with ventricular dysfunction. Relevant statements are found in the abstract:

> Many changing developmental properties of the pediatric myocardium and differences in the etiologies of ventricular dysfunction in children compared with adults [exist] ... invalidating the concept that children can safely be considered small adults for the purpose of understanding heart failure pathophysiology and treatment.

At page 2, the author states:

> The disease processes resulting in ventricular dysfunction are often different in children than adults. Many pediatric conditions have no close analogies in the adult ... [hence] the effects of intervention may be unlike those seen in adults.

And, at page 5, the author states:

> when trying to understand the proper therapy for children with ventricular dysfunction it is usually important not to view the child as a small adult and extrapolate the effects of ventricular dysfunction therapy for adult ischemia or post-infarction patients to the child where a multitude of non-ischemic, non post-infarction etiologies exist.

NINOS:

> At page 597 under "Conclusions" it states:
>
> Nitric oxide therapy reduced the use of extracorporeal membrane oxygenation, but had no apparent effect of mortality, in critically ill infants with hypoxic respiratory failure.

As set forth in the "Results" section on page 597, the study included 121 infants in the control group and 114 infants in the nitric oxide group. Left ventricular dysfunction was not mentioned.

> As to patient eligibility, NINOS states:
>
> Infants born at 34 or more weeks of gestation who required assisted ventilation for hypoxic respiratory failure and had an oxygenation index of at

> least 25 on two measurements made at least 15 minutes apart were eligible for the trial.
> Infants were considered ineligible for the study if they were more than 14 days old, had a congenital heart disease, or if it had been decided not to provide full treatment.

(P. 598 under "Study Patients").

Hayward 1996:

The ten patients (19 to 59 years old) in this study had severe LV dysfunction and secondary pulmonary hypertension. (See p. 81 under "Methods" and Results" headings). iNO was administered in 10, 20 and 40 ppm doses. (Id. at 2nd col.). The study concludes stating:

> Our results confirm the safety and utility of INO in short-term assessment of pulmonary hypertension in patients with severe cardiac impairment. The possibility of worsening cardiac function in some patients is worrisome, however, and suggests that INO should be used cautiously in such patients and only in combination with other treatments that have been shown to improve LV function. Safety guidelines for the use of INO were recently formulated. We recommend that these guidelines be expanded to include caution regarding the use of INO in patients with severe LV dysfunction. Further study of the haemodynamic effects of INO on the left ventricle is needed.

(P. 84).

Hayward 1997:

This study was conducted in eleven adults being 51-69 years old with normal LV function. (P. 49, under "Methods" heading). The objective of the study was to determine the effects of iNO on load-independent indexes of normal human LV function. (Id. under "Objectives" heading). The results were that iNO had no effect on steady state LV pressure, volume, contractility duration, active relaxation, diastolic compliance or PVR. (Id. under "Results" heading). Thus, it was concluded that 20 ppm of iNO does not significantly affect normal LV function. (Id. under "Conclusions" heading).

Roberts:

The study included 30 newborn infants having "severe hypoxemia even though they were receiving mechanical ventilation at an FiO_2 of 1.0" (p. 606 under "Criteria for Eligibility") to determine whether iNO decreases severe hypoxemia in infants with persistent pulmonary hypertension. (See Abstract and Results, p. 605). The study concluded that "[i]nhaled nitric oxide improves systemic oxygenation in infants with persistent pulmonary hypertension and may reduce the need for more invasive treatments." (See Conclusions, p. 605).

Roberts further states under the "Criteria for Eligibility" heading:

> Infants were excluded from the study if they had any of the following: previous treatment with extracorporeal membrane oxygenation or high-frequency oscillatory or jet ventilation, a congenital diaphragmatic hernia or suspected lung hypolasia, structural cardiac lesions (other than a patent ductus arteriosus), uncorrected hypotension (a mean aortic pressure below 40 mm Hg) or polycythemia (an arterial hematocrit of at least 70 percent), an unevacuated pneumothorax, or a phenotype consistent with a lethal chromosomal abnormality. Since infants who have received exogenous surfactant without sustain increases in systemic oxygenation have responses to inhaled nitric oxide similar to those of infants not previously treated with surfactant, they were not excluded from the study.

Loh:

This is a study of 19 patients with an average age of 52 +/- 3 years. (See p. 2780 under "Study Population" heading). These adult patients suffered from ischemic cardiomyapathy (heart failure due to coronary artery disease and resultant partial cardiac muscle death) and idiopathic dilated cardiomyopathy. (Id.). Fourteen of the patients were diagnosed with left ventricular dysfunction. (See p. 2780 under "Methods and Results" heading).

Loh discloses:

> The most prominent hemodynamic effect of NO inhalation was the increase in pulmonary artery wedge pressure (median increase 26%).
> Thus, more severe LV dysfunction (as evidenced by higher left heart filling pressures, lower stroke volume, and larger LV cavity size) was present in the

> patients who had the largest increases in pulmonary artery wedge pressure with inhaled NO.

(P. 2782 under "Hemodynamic Determinants of an Increase in Pulmonary Artery Wedge Pressure With Inhaled NO" heading).

Loh further discloses:

> The major finding of this study is that in patients with reactive pulmonary arterial hypertension secondary to LV failure, inhalation of NO causes reciprocal changes in the PVR (decrease) and LV filling pressure (increase). In contrast, in patients with LV failure, we found that inhalation of NO is associated not with a decrease in pulmonary artery pressure, but rather, with an increase in LV filling pressure that accounts for the decrease in PVR.

(P. 2783 under "Discussion" heading).

Inglessis 2004:

This is a study of 13 patients with an average age of 65 +/- 3 years. (See p. 793 under "Methods" heading). The objective of the study was to see if iNO improved "cardiac performance in patients with RVMI and CS." (See p. 794).

Under the "Methods" heading at p. 794, the reference discloses:

> Patients were then included for further study if their right atrial (RA) pressure was >10 mm Hg, their PCWP was no >5 mm Hg higher than the RA pressure, and their CI was <2.5 l/min/m^2. Patients were excluded from the study if they had severe pulmonary edema (PCWP >25 mm Hg; n=4), mechanical complications of MI requiring urgent surgical correction (N=0), severe mitral or aortic valvular disease (n=1), persistent hemodynamically significant tachyarrhythmias (n=1), or a history of clinically significant pulmonary disease (n=0).

The reference further discloses:

> In this study, PCWP did not change during NO inhalation by RVMI patients, as has been previously observed during administration to patients with severe LV systolic dysfunction. In patients with severe LV systolic dysfunction, which is usually accompanied by poor diastolic ventricular compliance, breathing NO is thought to increase pulmonary venous return, resulting in an increase in LV filling pressure. The RVMI patients in this study had primarily RV systolic and diastolic function, and the degree of LV dysfunction was not as severe as in

> those patients in whom the PCWP has been reported to increase during NO inhalation.

(P. 797, 2nd col.).

Inglessis 2005:

In a reply, the author states "[p]atients with severe LV systolic function should be monitored carefully during chronic NO inhalation because of the possibility of their developing pulmonary venous hypertension." (P. 965, 2nd col.).

Bocchi:

This study included 3 patients ages 40, 41, and 52 years old suffering from either ischemic or idiopathic cardiomyapathy. (P. 70, 1st col.). All three adults had severe pulmonary HTN and refractory heart failure and were candidates for cardiac transplantation. (Id.) All three patients were treated with iNO.

The reference discloses:

> Results of this investigation demonstrate that acute inhaled nitric oxide produces rapid pulmonary vasodilation in the absence of hypoxia in patients with severe heart failure. However, nitric oxide inhalation was associated with an increment in pulmonary pressure, mainly pulmonary wedge pressure, and an improvement in cardiac output. In addition, inhaled nitric oxide may lead to pulmonary edema in patients with severe heart failure.

(P. 71, 1st col.).

Cujec:

This is a case study involving 33 adults with a mean age of 69 +/- 11 years, most of whom had significant valvular disease and dysfunctional LV characterized by a reduced ejection fraction. (P. 816 under "Patients" heading, and p. 819 under "Results" heading).

Cujec concludes at page 823 stating:

> We found in a randomized and blinded trial that the reduction in pulmonary artery systolic pressure following nitric oxide inhalation depends on the pre-existing LVEF. Our results in patients with a broader mix of cardiac pathology confirm previous case series. These observations suggest further limitations for the clinical role of inhaled nitric oxide. We postulate that in patients with the

> least cardiac reserve, decreasing venous but not arterial pulmonary vascular resistance may cause an increase in regional pulmonary edema. Through reflex mechanisms, this could further impair cardiopulmonary function resulting in cardiac decompensation, worsening pulmonary hypertension and generalized pulmonary edema. This study cautions against the ubiquitous use of inhaled nitric oxide in the treatment of all critically ill patients. Nitric oxide is not just a pulmonary vasodilator but has profound effects on many other systems. The adverse effects of nitric oxide may become most evident in patients with the least cardiac reserve.

Rosales:

This is a case report of a one-month old neonate that developed rebound pulmonary hypertension after receiving iNO. (See Abstract at p. 224). The infant patient was diagnosed with total anomalous pulmonary venous return (three pulmonary veins draining into the portal system below the diaphragm and the remaining upper left pulmonary vein draining into the innominate vein). (Id.).

This infant underwent surgical correction and in the post operative period received iNO. (See p. 225, 1st col.). iNO was discontinued based on the rationale that the episode of pulmonary HTN may have been caused by left atrial hypertension secondary to a sudden increase in pulmonary blood flow into a non-compliant left atrium and ventricle due in part to the redirection of blood flow from the surgical correction. (See p. 225, 2nd col.).

Argenziano:

This study in pigs resulted in the following conclusion:

> In conclusion, we have reproduced, in a porcine model of heart failure and pulmonary hypertension, the constellation of clinically observed hemodynamic responses to inhaled NO therapy, including dose-dependent decreases in pulmonary arterial pressure and PVR and increases in LVEDP. Furthermore, determination of the ESPVR, PRSW, EDPVR, and T in these animals has demonstrated no effect of inhaled NO on myocardial contractility or relaxation. An alternative explanation that has been proposed on theoretical grounds is that volume shifts caused by pulmonary vasodilation are responsible for clinically observed elevations in left atrial pressure and may also explain why patients with preexisting ventricular dysfunction are at greatest risk for these pressure elevations. Although clinical validation of our findings in humans is necessary and is the subject of current investigations, an understanding of this

> mechanism may lead to strategies allowing the safe use of inhaled NO in heart failure, perhaps by adjunctive vasodilator therapy.

(P. 707).

Steinhorn 2007:

This is a review article of persistent pulmonary HTN. It is a general discussion and review, not a clinical study. No data is provided. It points out that iNO is contraindicated in congenital heart disease (e.g., interrupted AO arch, critical AO stenosis, and hypolplastic LV) and severe LV dysfunction.

Under the heading "Treatment with iNO," it states:

> Treatment with iNO for newborns with an OI>25. Nitric oxide (NO) is an endothelial-derived gas signaling molecule that relaxes vascular smooth muscle and that can be delivered to the lung by means of an inhalation device (INOVent; Datex-Ohmeda Ind, Madison, WI).
> In 2 large randomized trials, NO reduced the need for ECMO support by approximately 40%.
> Contraindications to iNO include congenital heart disease characterized by left ventricular outflow tract obstruction (eg, interrupted aortic arch, critical aortic stenosis, hypoplastic left heart syndrome) and severe left ventricular dysfunction.

Krasuski:

This reference reports the results of a clinical study in forty-two adult patients (26 to 77 years old) having pulmonary hypertension during cardiac catheterization and receiving iNO. (See Abstract, p. 2204). The reference concludes that

> Nitric oxide is a safe and effective screening agent for pulmonary vasoreactivity. Regardless of etiology of pulmonary hypertension, pulmonary vasoreactivity is frequently demonstrated with the use of NO. Right ventricular diastolic dysfunction may predict a poor vasodilator response.

(Id. under "Conclusions" heading).

Semigran:

This study included 16 adults (13 men and 3 women) having a mean age of 51 ± 2 years each having class III or IV heart failure and being considered for heart

transplantation. (See p. 983, 1st col.). No patient had a history of primary pulmonary disease, and pulmonary function testing was consistent with chronic left heart failure. (Id.). The patients were treated with digoxin, diuretic drugs, vasodilators and amiodarone. (Id.) iNO was administered at 20, 40 and 80 ppm. (Id. at 2nd col.).

The reference concludes stating:

> Inhaled nitric oxide is a selective pulmonary vasodilator in patients with severe chronic heart failure. The selectivity of inhaled nitric oxide for the pulmonary circulation offers a potential advantage over nonselective vasodilators such as nitroprusside in the identification of reversible pulmonary vasoconstriction in potential heart transplant recipients. Nitric oxide increases left ventricular filling pressure in patients with severe heart failure by an unknown mechanism.

(P. 982 under "Conclusions" heading).

Dickstein:

The reference teaches mathematical (see Appendix at p. 720) and electric circuit (see Figure 1 at p. 717) models of a cardiovascular system as "time varying elastances: the pulmonary and systemic vascular systems were each modeled as a series of resistive and compliance elements." (P. 715 under "Methods" heading).

The reference concludes stating:

> Pulmonary vasodilation by itself can lead to an increase in pulmonary venous pressure that is mediated by shifts of blood between arterial and venous compartments of the pulmonary bed. Furthermore, impairment in ventricular contractile state by itself has relatively little effect on pulmonary venous pressure. The magnitude of the increase in pulmonary venous pressure is largely determined by the volume status and the initial value of pulmonary vascular resistance.

(P. 715 under "Conclusions" heading).

Dickstein further discloses:

> The present analysis suggests that it is not necessary for this agent [i.e., nitric oxide] to work as a negative inotrope to cause pulmonary venous pressure to rise: its pulmonary vasodilating actions alone are sufficient to explain why patients with preexisting heart failure are at greatest risk for pulmonary edema.

(P. 719, 2nd col.).

Henrichsen:

This reference is a letter to the editor of journal reporting iNO treatment of a baby born at 38 weeks of gestation diagnosed with persistent pulmonary hypertension of the newborn (PPHN) and severe left ventricular dysfunction. The baby was treated with 20 ppm iNO which "resulted in an immediate fall in the mean systemic arterial blood pressure from 48 to 35 mm Hg, which reversed when the NO therapy was discontinued." In other words, the iNO caused systemic hypotension.

As second iNO treatment thirty hours later "resulted in a marked improvement in oxygenation, from an arterial oxygen tension to 16 to 420 mm Hg without a change in the systemic arterial blood pressure."

Ovodov:

The review article discusses various clinical studies of PPHN using iNO. (P. 95, 2nd col.). In particular, the reference cites the NINOS trial. (Id.) It concludes that "[s]afety of low-dose inhaled nitric oxide in newborns has been suggested by several studies" and that "there are no reports of any related adverse clinical manifestations." (P. 96, 1st col.).

Adatia:

This reference reports the results of a study involving 11 patients ranging in age from 0.7 to 27 years with a median of 13 years diagnosed with pulmonary hypertension. (P. 1656, 2nd col.). Some of the patients were diagnosed with "severe left ventricular failure despite optimal medical management with digoxin, diuretic drugs and, when appropriate, maximal afterload reduction therapy." (P. 1657, 1st col.).

The reference concludes stating:

> These preliminary observations suggest that nitric oxide is a potent pulmonary vasodilator with minimal systemic effects. It may be useful in discriminating patients needing combined heart and lung transplantation from those requiring exchange of the heart alone.

(P. 1656 under Conclusions heading).

Findlay:

This reference is a case report concerning a 22-year old man treated with iNO where the patient had a "paradoxical response to inhaled nitric oxide, where a rise in mean pulmonary artery and pulmonary artery occlusion pressure and a fall in cardiac output and stroke volume occurred, in a young man with *meningococcaemia*." (P. 134, 1st col.).

Henrichsen is a report of a single near-term neonate having PPHN and LVD that experienced systemic hypotension when treated with iNO, which is contrary to the accepted understanding that is a selective vasodilator, i.e., non-systemic. Moreover, the subsequent iNO treatment had a positive therapeutic outcome. Henrichsen fails to teach LVD as exclusionary criteria in the claimed patient population, and it teaches away from the invention by merely cautioning iNO treatment.

The instant claims are patentable over Ovodov, Adatia and Findlay at least because each reference fails to teach or suggest excluding the claimed patient population having LVD from being treated with iNO.

9(C) Detailed Explanation of Patentability

None of the references disclose excluding from iNO treatment any patient in the patient population (comprising a neonate or near-term neonate) that have been diagnosed as having pre-existing left ventricular dysfunction (LVD) in order to avoid adverse events or serious adverse events. (See independent claims 1, 6, 13 and 17). Thus, independent claims 1, 6, 13 and 17 are patentably novel and nonobvious over the listed most relevant references as well as the other references of record. Moreover,

dependent claims 2-5, 7-12, 14-16 and 18-20 are patentably novel and nonobvious for at least the same reasons set forth herein respecting independent claims 1, 6, 13 and 17.

The AAP reference is highly relevant due to the prominence of the Pediatric Committee. The fact that it is silent respecting excluding from iNO treatment any child patient diagnosed with pre-existing left ventricular function speaks louder than words.

Lipshultz teaches that data and information gleaned from iNO studies in adults do not correlate or are otherwise probative of iNO studies in children. Thus, the Hayward 1996 & 1997, Loh, Inglessis 2004 & 2005, Bocchi, Cujec, Krasuski, Findlay and Semigran references are not probative of the instantly claimed invention.

Pre-existing LVD is not mentioned in the NINOS reference involving infants. While the Roberts involves neonate patients, it fails to teach excluding such patients if they have been diagnosed with pre-existing LVD.

Rosales involves a one-month old neonate patient undergoing surgical correction and post operative iNO treatment. Rosales also fails to teach or suggest pre-existing LVD as exclusionary criteria for iNO treatment.

Argenziano is a pig study that also fails to teach or suggest pre-existing LVD as exclusionary criteria for iNO treatment.

Steinhorn 2007 is a general discussion and review. No data is provided. Therefore, Steinhorn 2007 is a non-enabling reference.

Dickstein is a "purely theoretic analysis of the impact of NO therapy on pulmonary venous pressure." (P. 719, 2nd col.). The reference fails to disclose any data to support this unpredictable science which is also not well understood, therefore, Dickstein is non-enabling prior art. The reference also teaches away from excluding a patient from being treated with iNO where the patient has been diagnosed with pre-existing LVD. For example, the reference theorizes that increased volume causes the risk of adverse events stating:

> results of the present analysis would suggest that patients with heart failure are at increased risk for development of pulmonary edema during NO therapy because of the high effective volume status.

(P. 719, 2nd col.).

Henrichsen is a report of a single near-term neonate having PPHN and LVD that experienced **systemic** hypotension when treated with iNO, which is contrary to the accepted understanding that nitric oxide is a selective vasodilator, i.e., non-systemic. Moreover, the subsequent iNO treatment had a positive therapeutic outcome. Henrichsen fails to teach LVD as exclusionary criteria in the claimed patient population, and it teaches away from the invention by merely cautioning iNO treatment.

The instant claims are patentable over Ovodov, Adatia and Findlay at least because each reference fails to teach or suggest excluding the claimed patient population having LVD from being treated with iNO.

9(D) Concise Statement of Utility

The instantly claimed invention is eligible subject matter under 35 USC 101 for patentable utility in that the claims are generally directed to a method of excluding patients in need of being treated with inhaled nitric oxide. The purpose of such mandatory exclusion is to reduce the incidence of adverse events or serious adverse events. Patients in an intended patient population are excluded from such treatment (even though the inhaled nitric oxide treatment would be potentially beneficial to the patient) if the patient has pre-existing left ventricular dysfunction.

9(E) Showing of Support under 35 USC 112, First Paragraph

Support and antecedent basis for the claimed invention is found at least in the SUMMARY OF THE INVENTION as originally filed at pages 2-4 and ¶¶[0005]-[0020]. Enablement of the claimed invention is found at least in the DETAILED DESCRIPTION OF THE EXEMPLARY EMBODIMENTS at pages 4-13 and ¶¶[0021]-[0050] as well as in EXAMPLE1: INOT22 STUDY at pages 13-22 and ¶¶[0051]-[0069].

9(F) Identification of References Disqualified as Prior Art under 35 USC 103(c)

None of the cited references are disqualified as prior art under 35 USC 103(c).

Respectfully Submitted,

Christopher P. Rogers, Reg. No. 36,334

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EXHIBIT N

UNITED STATES PATENT AND TRADEMARK 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

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EXAMINER	
ARNOLD, ERNST V	
ART UNIT	PAPER NUMBER
1613	
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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

EXHIBIT O

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

EXHIBIT P

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

EXHIBIT Q

UNITED STATES PATENT AND TRADEMARK OFFICE

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

EXHIBIT R

Notice of Allowability	Application No. 12/821,020	Applicant(s) BALDASSARRE ET AL.	
	Examiner ERNST ARNOLD	Art Unit 1613	

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

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

1. ☒ This communication is responsive to *8/15/12*.
2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.
3. ☒ The allowed claim(s) is/are *31-42,46-49 and 51-63*.
4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
   a) ☐ All b) ☐ Some* c) ☐ None of the:
      1. ☐ Certified copies of the priority documents have been received.
      2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
      3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.

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

5. ☐ A SUBSTITUTE OATH OR DECLARATION must be submitted. Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL PATENT APPLICATION (PTO-152) which gives reason(s) why the oath or declaration is deficient.
6. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   (a) ☐ including changes required by the Notice of Draftsperson's Patent Drawing Review (PTO-948) attached
      1) ☐ hereto or 2) ☐ to Paper No./Mail Date _____.
   (b) ☐ 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).
7. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☐ Notice of Draftperson's Patent Drawing Review (PTO-948)
3. ☐ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date _____
4. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
5. ☐ Notice of Informal Patent Application
6. ☐ Interview Summary (PTO-413), Paper No./Mail Date _____ .
7. ☐ Examiner's Amendment/Comment
8. ☒ Examiner's Statement of Reasons for Allowance
9. ☐ Other _____.

/Ernst V Arnold/
Primary Examiner, Art Unit 1613

DETAILED ACTION

Claims 1-30, 43-45 and 50 have been cancelled. Claims 31-42, 46-49 and 51-63 are pending and under examination.

Withdrawn rejections:

Applicant's amendments and arguments filed 8/15/12 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. Claims 31-42 and 46-63 were rejected under 35 U.S.C. 103(a) as being unpatentable over Davidson et al. (Pediatrics 1998, 101 (3) pp 325-334) and The Neonatal Inhaled Nitric Oxide Study Group (The New England Journal of Medicine 1997, 336(9), pp597-604) and Macrae (Semin Neonatal 1997, 2, 49-58) and Miller et al. (Achives of Disease in Childhood 1994, 70, F47-F49) and Weinberger et al. (Toxicology Sciences 2001, 59, 5-16) and Hurford et al. (Nitric Oxide: Biology and Pathobiology 2000 Academic Press, Chapter 56, pages 931-945) and Kazerooni et al. (Cardiopulmonary Imaging 2004, Lippincott Williams & Wilkins, pp 234-235) and Wheeler et al. (Pediatric Critical Care Medicine 2007, Springer, page 278) and Moss et al. (Moss And Adams' Heart Disease in Infants, Children, and Adolescents, 2007, vol. 1, page 991 in part) and Bocchi et al. The American Journal of Cardiology 1994, 74, pp: 70-72. 4 pages) and Fraisse et al. (Cardiol Young 2004; 14: 277-283 IDS filed on 12/27/11) and Loh et al. (Circulation 1994, 90; 2780-2785; of record) and Atz et al. (Seminars in Perinatology 1997, 21(5), pp

441-455; of record) and Ichinose et al. (Circulation 2004; 109:3106-3111: IDS filed on 1/10/12). Applicant's amendments and arguments are sufficient to overcome the rejection and it is withdrawn by the Examiner.

Terminal Disclaimer

The terminal disclaimer filed on 8/15/12 disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of copending applications 12/820866 and 12/821041 has been reviewed and is accepted. The terminal disclaimer has been recorded.

Allowable Subject Matter

The following is an examiner's statement of reasons for allowance: the cited art of record does not teach or suggest, alone or in combination, the patient population of a child in need of the administration of 20 ppm iNO and determining the PCWP as greater than or equal to 20 mm Hg in the method as instantly claimed to reduce the risk of occurrence of pulmonary edema.

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

Conclusion

Claims 31-42, 46-49 and 51-63 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

EXHIBIT S

Attorney Docket No.: 26047-0003004 / 3000-US-0008CON3

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	: James S. Baldassarre et al.	Art Unit :	1613
Serial No.	: 12/821,020	Examiner :	Ernst V. Arnold
Filed	: June 22, 2010	Confirmation No.:	3179
		Notice of Allowance Date: August 31, 2012	
Title	: METHODS OF REDUCING THE RISK OF OCCURRENCE OF PULMONARY EDEMA IN CHILDREN IN NEED OF TREATMENT WITH INHALED NITRIC OXIDE		

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

RESPONSE TO NOTICE OF ALLOWANCE
AND
COMMENTS ON STATEMENT OF REASONS FOR ALLOWANCE

In response to the Notice of Allowance mailed August 31, 2012, enclosed is a completed issue fee transmittal form PTOL-85b.

The Notice of Allowance indicates a title for this application that is incorrect. On December 27, 2011, Applicant filed an Amendment in Reply to Final Action of June 27, 2011, in which the title was amended to read: "**Methods of reducing the risk of occurrence of pulmonary edema in children in need of treatment with inhaled nitric oxide**." Applicant asks that the Office's records be corrected to reflect the title as amended on December 27, 2011, and that the correct title be printed on the face of the patent.

Comments on Statement of Reasons for Allowance

Applicant notes that the Examiner's statement of reasons for allowance provided on page 3 of the Notice of Allowability mailed August 31, 2012, are just some of many reasons that the present claims are allowable over the cited art of record.

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.

August 31, 2012
Date of Deposit or Transmission

/Nancy Bechet/
Signature

Nancy Bechet
Typed or Printed Name of Person Signing Certificate

The large entity issue fee of $1740 and publication fee of $300 are being paid concurrently with this filing. If there are any other necessary charges, or any credits, please apply them to Deposit Account 06-1050, referencing the above attorney docket number.

Respectfully submitted,

Date: August 31, 2012

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

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22904107.doc

EXHIBIT T

Trials@uspto.gov
571.272.7822

Paper 12 (IPR2015-00522)
Paper 12 (IPR2015-00524)
Paper 12 (IPR2015-00525)
Paper 12 (IPR2015-00526)
Entered: July 29, 2015

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

PRAXAIR DISTRIBUTION, INC.,
Petitioner,

v.

INO THERAPEUTICS, INC.,
Patent Owner.

Case IPR2015-00522 (8,282,966 B2)
Case IPR2015-00524 (8,293,284 B2)
Case IPR2015-00525 (8,431,163 B2)
Case IPR2015-00526 (8,795,741 B2)[1]

Before LORA M. GREEN, TINA E. HULSE, and ROBERT A. POLLOCK, *Administrative Patent Judges*.

HULSE, *Administrative Patent Judge*.

DECISION
Denying Institution of *Inter Partes* Review
37 C.F.R. § 42.108

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[1] This Decision addresses issues that are common to each of the above-referenced cases. We, therefore, issue a single Decision that has been entered in each case. The parties may use this style caption when filing a single paper in multiple proceedings, provided that such caption includes a footnote attesting that "the word-for-word identical paper is filed in each proceeding identified in the caption."

I. INTRODUCTION

Petitioner, Praxair Distribution, Inc., filed Petitions requesting an *inter partes* review of: (1) claims 1–29 of U.S. Patent No. 8,282,966 ("the '966 patent") (Ex. 1001, IPR2015-00522); (2) claims 1–30 of U.S. Patent No. 8,293,284 B2 ("the '284 patent") (Ex. 1001, IPR2015-00524); (3) claims 1–25 of U.S. Patent No. 8,431,163 B2 ("the '163 patent") (Ex. 1001, IPR2015-00525); and (4) claims 1–44 of U.S. Patent No. 8,795,741 B2 ("the '741 patent") (Ex. 1001, IPR2015-00526). Paper 1 (IPR2015-00522) ("-522 Pet.").[2] Patent Owner, INO Therapeutics LLC, filed a Preliminary Response to each Petition. Paper 8 (IPR2015-00522) ("-522 Prelim. Resp.").[3]

We have jurisdiction under 35 U.S.C. § 314, which provides that an *inter partes* review may not be instituted "unless . . . there is a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition." 35 U.S.C. § 314(a). Upon considering the Petitions and Preliminary Responses, we determine that Petitioner has not established a reasonable likelihood that it would prevail in showing the unpatentability of any of the challenged claims in any of the proceedings. Accordingly, the Petition in each proceeding is *denied*.

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[2] Petitioner filed Petitions as Paper 1 in each of the other proceedings. We refer to those Petitions as "-524 Pet.," "-525 Pet.," and "-526 Pet."

[3] Patent Owner filed Preliminary Responses as Paper 8 in each of the other proceedings. We refer to those Preliminary Responses as "-524 Prelim. Resp.," "-525 Prelim. Resp.," and "-526 Prelim. Resp."

A. Related Proceedings

Petitioner states that it is not aware of any current litigation involving any of the involved patents. -522 Pet. 7.[4]

B. The Involved Patents

The involved patents are all related and share substantially the same Specification. The Specification discloses methods of reducing the risk of an adverse event, such as pulmonary edema, associated with treating a patient with inhaled nitric oxide gas ("iNO"). Ex. 1001, Abstract. Nitric oxide is a lung-specific vasodilator that significantly improves blood oxygenation and reduces the need for extracorporeal oxygenation. *Id.* at 3:33–42. INOmax®—nitric oxide for inhalation—is an FDA-approved drug for treatment of term and near term (>34 weeks gestation) neonates who have hypoxic respiratory failure associated with evidence of pulmonary hypertension, known as persistent pulmonary hypertension in the newborn ("PPHN"). *Id.* at 1:18–22, 6:23–29.

The Specification also describes the INOT22 Study, which was conducted, in part, to assess the safety and effectiveness of INOmax® in patients four weeks to eighteen years of age undergoing assessment of pulmonary hypertension. *Id*. at 9:18–30, 43–44. Initially, the study protocol did not include a baseline pulmonary capillary wedge pressure ("PCWP") value as an exclusion criteria.[5] *Id.* at 12:25–26. During the study, at least

---

[4] Petitioner makes similar arguments in its papers and cites similar evidence in each of the cases. Accordingly, citations to papers and exhibits in this Decision refer to those filed in IPR2015-00522, unless stated otherwise.

[5] PCWP provides an estimate of left atrial pressure, which may be used to diagnose the severity of left ventricular dysfunction and to measure pulmonary hypertension. Ex. 1001, 5:9–18.

two patients developed signs of pulmonary edema. *Id.* at 13:2–3. The Specification states that "[t]his is of interest because pulmonary edema has previously been reported with the use of iNO in patients with LVD [left ventricular dysfunction], and may be related to decreasing PVR [pulmonary vascular resistance] and overfilling of the left atrium." *Id.* at 13:3–6. The Specification further states that "after the surprising and unexpected identification of SAEs [serious adverse events] in the early tested patients, it was determined that patients with pre-existing LVD had an increased risk of experiencing an AE or SAE [such as pulmonary edema] upon administration." *Id.* at 12:26–30, 13:62–64. The study protocol was amended to exclude patients with a baseline PCWP greater than 20 mmHg, which was selected to avoid enrolling children with LVD who "would be most likely at-risk for these SAEs." *See id*. at 12:32–38.

C. Illustrative Claim

Petitioner challenges: (1) claims 1–29 the '966 patent (IPR2015-00522); (2) claims 1–30 of the '284 patent (IPR2015-00524); (3) claims 1–25 of the '163 patent (IPR2015-00525); and (4) claims 1–44 of the '741 patent (IPR2015-00526). The challenged claims are all similar. Claim 1 of the '966 patent is illustrative and is reproduced below:

> 1. A method of reducing the risk of occurrence of pulmonary edema associated with a medical treatment comprising inhalation of 20 ppm nitric oxide gas, said method comprising:
>
> (a) performing echocardiography to identify a child in need of 20 ppm inhaled nitric oxide treatment for pulmonary hypertension, wherein the child is not dependent on right-to-left shunting of blood;
>
> (b) determining that the child identified in (a) has a pulmonary capillary wedge pressure greater than or equal to 20 mm Hg and thus has left ventricular dysfunction, so

> is at particular risk of pulmonary edema upon treatment with inhaled nitric oxide; and
>
> (c) excluding the child from inhaled nitric oxide treatment, based on the determination that the patient has left ventricular dysfunction and so is at particular risk of pulmonary edema upon treatment with inhaled nitric oxide.

Common among almost all the independent claims of all the involved patents is a limitation like step (c) of claim 1 above, which excludes a patient from treatment with inhaled nitric oxide based on a determination that the patient has left ventricular dysfunction and so is at particular risk of pulmonary edema upon treatment with inhaled nitric oxide. *See* claims 1(c),[6] 6(c), 13(e), and 22(e) of the '966 patent (Ex. 1001, IPR2015-00522); claims 1(c), 6(c), 13(e), and 23(e) of the '284 patent (Ex. 1001, IPR2015-00524); claims 1(c) and 6(e) of the '163 patent (Ex. 1001, IPR2015-00525); claims 1(e) and 34(e) of the '741 patent (Ex. 1001, IPR2015-00526).

However, not all of the independent claims recite the exact language as claim 1(c) above. Certain claims recite excluding a patient from treatment with inhaled nitric oxide or, despite the patient's ongoing need for treatment for hypoxic respiratory failure, discontinuing treatment with inhaled nitric oxide after it has begun, where the exclusion or discontinuation is based on a determination that the patient has left ventricular dysfunction and so is at particular risk of pulmonary edema upon treatment with inhaled nitric oxide. *See* claims 12(c) and 20(e) of the '163 patent (Ex. 1001, IPR2015-00525); claims 9(e) and 37(e) of the '741 patent

[6] For ease of reference, we refer to particular steps of particular claims, e.g., step (c) of claim 1, as "claim 1(c)."

(Ex. 1001, IPR2015-00526). Additionally, claim 24 of the '741 patent recites "(d) determining that a second patient . . . has pre-existing left ventricular dysfunction, so is at particular risk of increased PCWP leading to pulmonary edema upon treatment with inhaled nitric oxide" and then "(e) administering a second treatment regimen to the second patient [determined to have LVD], wherein the second treatment regimen does not comprise either (i) administration of inhaled nitric oxide for 14 days or (ii) administration of inhaled nitric oxide until the second patient's hypoxia has resolved." Ex. 1001, claim 24 (IPR2015-00526).

Despite the differences in claim language, we interpret the above "exclusion limitations" to all require excluding a patient from inhaled nitric oxide treatment—either by never treating the patient or discontinuing treatment—after determining that the patient has left ventricular dysfunction and so is at particular risk of pulmonary edema upon treatment with inhaled nitric oxide.

D. The Asserted Grounds of Unpatentability

In IPR2015-00522, Petitioner challenges the patentability of claims 1–29 of the '966 patent on the following grounds (-522 Pet. 14–58):

References	**Basis**	**Claims Challenged**
Bernasconi,[7] INOmax label,[8] Loh,[9] and Goyal[10]	§ 103	1–3, 5–9, 11, 13–17, 20, 22–25, and 28

[7] A. Bernasconi and M. Beghetti, *Inhaled Nitric Oxide Applications in Paediatric Practice*, 4 IMAGES PAEDIATR. CARDIOL. 4–29 (2002) (Ex. 1004).

[8] Final Printed Labeling for INOmax™ (nitric oxide) for inhalation (Ex. 1014).

IPR2015-00522 (8,282,966 B2); IPR2015-00524 (8,293,284 B2); IPR2015-00525 (8,431,163 B2); IPR2015-00526 (8,795,741 B2)

References	Basis	Claims Challenged
Bernasconi, INOmax label, Loh, Goyal, and Macrae[11]	§ 103	4, 10, 12, 18, 19, 21, 26, 27, and 29
Ichinose,[12] Neonatal Group,[13] Macrae, Loh, Goyal, and Germann[14]	§ 103	1–29

In IPR2015-00524, Petitioner challenges the patentability of claims 1–30 of the '284 patent on the following grounds (-524 Pet. 12–56):

References	Basis	Claims Challenged
Bernasconi, INOmax label, Loh, and Goyal	§ 103	1–3, 5–9, 11, 13, 14, 16–18, 21, 23–27, and 29
Bernasconi, INOmax label, Loh, Goyal, and Macrae	§ 103	4, 10, 12, 15, 19, 20, 22, 28, and 30

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[9] E. Loh et al., *Cardiovascular Effects of Inhaled Nitric Oxide in Patients with Left Ventricular Dysfunction*, 90 CIRCULATION 2780–85 (1994) (Ex. 1006).

[10] P. Goyal et al., *Efficacy of Nitroglycerin Inhalation in Reducing Pulmonary Arterial Hypertension in Children with Congenital Heart Disease*, 97 BRITISH J. ANESTHESIA 208–14 (2006) (Ex. 1007).

[11] D. J. Macrae et al., *Inhaled Nitric Oxide Therapy in Neonates and Children: Reaching a European Consensus*, 30 INTENSIVE CARE MED. 372–80 (2004) (Ex. 1008).

[12] F. Ichinose et al., *Inhaled Nitric Oxide: A Selective Pulmonary Vasodilator: Current Uses and Therapeutic Potential*, 109 CIRCULATION 3106–11 (2004) (EX. 1009).

[13] The Neonatal Inhaled Nitric Oxide Study Group, *Inhaled Nitric Oxide in Full-Term and Nearly Full-Term Infants with Hypoxic Respiratory Failure*, 336 NEW ENG. J. MED. 597–604 (1997) (Ex. 1011).

[14] P. Germann et al., *Inhaled Nitric Oxide Therapy in Adults: European Expert Recommendations*, 31 INTENSIVE CARE MED. 1029–41 (2005) (EX. 1010).

IPR2015-00522 (8,282,966 B2); IPR2015-00524 (8,293,284 B2); IPR2015-00525 (8,431,163 B2); IPR2015-00526 (8,795,741 B2)

References	Basis	Claims Challenged
Ichinose, Neonatal Group, Macrae, Loh, Goyal, and Germann	§ 103	1–30

In IPR2015-00525, Petitioner challenges the patentability of claims 1–25 of the '163 patent on the following grounds (-525 Pet. 12–54):

References	Basis	Claims Challenged
Bernasconi, INOmax label, Loh, and Goyal	§ 103	1, 2, 4, 6, 7, 9, 11–13, 15, 18, 20, 21, 23, and 25
Bernasconi, INOmax label, Loh, Goyal, and Macrae	§ 103	3, 5, 8, 10, 14, 16, 17, 19, 22, and 24
Ichinose, Macrae, Germann, Neonatal Group, Loh, and Goyal	§ 103	1–25

In IPR2015-00526, Petitioner challenges the patentability of claims 1–44 of the '741 patent on the following grounds (-526 Pet. 13–60):

References	Basis	Claims Challenged
Bernasconi, Loh, and Goyal	§ 103	1, 2, 4, 6–14, 17–23, 31, 32, 34–35, 37–40, and 42–44
Bernasconi, Loh, INOmax label, Juliana,[15] and Goyal	§ 103	24–27, 29, 30, and 33
Bernasconi, Loh, Macrae, and Goyal	§ 103	3, 5, 15, 16, 36, and 41
Bernasconi, Loh, INOmax label, Juliana, Macrae, and Goyal	§ 103	28

[15] A. Juliana and F. Abbad, *Severe Persistent Pulmonary Hypertension of the Newborn in a Setting Where Limited Resources Exclude the Use of Inhaled Nitric Oxide: Successful Treatment with Sildenafil*, 164 EUR. J. PEDIATR. 626–29 (2005) (Ex. 1032, IPR2015-00526).

IPR2015-00522 (8,282,966 B2); IPR2015-00524 (8,293,284 B2);
IPR2015-00525 (8,431,163 B2); IPR2015-00526 (8,795,741 B2)

References	Basis	Claims Challenged
Ichinose, Neonatal Group, Macrae, Loh, Germann, and Goyal	§ 103	1–23, 31, 32, and 34–44
Ichinose, Neonatal Group, Macrae, Loh, INOmax label, Germann, and Goyal	§ 103	24–30 and 33

II. ANALYSIS

A. Claim Construction

In an *inter partes* review, the Board interprets claim terms in an unexpired patent according to the broadest reasonable construction in light of the specification of the patent in which they appear. *See In re Cuozzo Speed Techs., LLC*, No. 2014-1301, 2015 WL 4097949, at *5–*8 (Fed. Cir. July 8, 2015); 37 C.F.R. § 42.100(b). Under that standard, and absent any special definitions, we give claim terms their ordinary and customary meaning, as would be understood by one of ordinary skill in the art at the time of the invention. *See In re Translogic Tech., Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007). Any special definitions for claim terms must be set forth with reasonable clarity, deliberateness, and precision. *See In re Paulsen*, 30 F.3d 1475, 1480 (Fed. Cir. 1994).

1. "child" and "children"

The term "child" or "children" appears in each of the independent claims of the '966 patent and independent claims 34 and 37 of the '741 patent. Ex. 1001, claims 1, 6, 13, and 22 (IPR2015-00522); Ex. 1001, claims 34 and 37 (IPR2015-00526).

Petitioner asserts that the Specification states that "the term 'children' (and variations thereof) ***includes*** those being around 4 weeks to 18 years of age." -522 Pet. 10 (quoting Ex. 1001, 4:13–14). Given the word "includes,"

Petitioner argues that the term "children" is not limited to children in that age range. Additionally, Petitioner notes that dependent claims 2 and 8 specify that "the child is a neonate," therefore confirming that the age range for a "child" is broader than the range stated in the Specification. *Id.*

Patent Owner argues that the term "child" does not include human beings prior to birth. -522 Prelim. Resp. 21. Patent Owner also notes that the Specification defines adults as "those over 18 years of age." *Id.* (quoting Ex. 1001, 4:15–16). Because the Specification defines patients who are over 18 years of age as adults, Patent Owner contends that the terms "child" and "children" should be construed to mean "humans from birth until 18 years of age." *Id.* at 23.

We find Patent Owner's arguments persuasive and determine that Patent Owner's proposed construction is the broadest reasonable interpretation in light of the Specification.

2. "term or near-term neonate"

The claim phrase "term or near-term neonate" appears in each of the independent claims of the '284 patent and the '163 patent. Ex. 1001, claims 1, 6, 13, and 23 (IPR2015-00524); Ex. 1001, claims 1, 6, 12, and 20 (IPR2015-00525). The phrase also appears in independent claims 1, 9, and 24 of the '741 patent. Ex. 1001, claims 1, 9, and 24 (IPR2015-00526).

Petitioner does not offer a specific construction for this term. Patent Owner, however, relies on the Specification and medical dictionary definitions to assert the following constructions for the following terms: (1) "neonate" is "an infant aged 1 month or younger"; (2) "near-term" is "greater than around 34 weeks gestation"; and (3) "term" is "between around 37 and around 40 weeks gestation." -524 Prelim. Resp. 21–22. Specifically, Patent Owner notes that the Specification states that "near term neonates"

are those having achieved "> 34 weeks gestation." *Id.* at 21 (citing -524 Ex. 1001, 6:27–28). Patent Owner also provides medical dictionary definitions for the term "infant" and "neonate" that are consistent with its proposed constructions. *Id.* (citing Ex. 2007, 967–68, 1288).

We find Patent Owner's arguments persuasive and determine that Patent Owner's proposed constructions are the broadest reasonable interpretation in light of the Specification. That is, we construe the phrase "term or near-term neonate" to mean "an infant aged 1 month or younger born between around 37 and 40 weeks gestation or greater than around 34 weeks gestation."

B. Obviousness of the '966 Patent, the '284 Patent, the '163 Patent, and certain of the '741 Patent Claims over Bernasconi, INOmax Label, Loh, and Goyal

Petitioner asserts that each of the independent claims in the '966 patent, the '284 patent, and the '163 patent is unpatentable as obvious over Bernasconi, INOmax label, Loh, and Goyal. -522 Pet. 14–32. Petitioner also asserts that independent claims 1, 9, 34, and 37 of the '741 patent are unpatentable as obvious over Bernasconi, Loh, and Goyal. -526 Pet. 13–25. As support, Petitioner submits the testimony of Dr. Maurice Beghetti in each proceeding. Ex. 1002. Patent Owner opposes Petitioner's assertions. *See, e.g.*, -522 Prelim. Resp. 35–50. We determine, on the current record, that Petitioner has not established a reasonable likelihood that it would prevail in showing any of those challenged claims is unpatentable as obvious over the cited prior art.

1. Bernasconi (Ex. 1004)

Bernasconi reviews the "delivery and monitoring aspects of inhaled nitric oxide, its potential toxic and side effects and its applications in several

cardiopulmonary disorders in paediatrics." Ex. 1004, Abstract; *see also* Title. Bernasconi states that "[d]ose response studies have been performed in persistent pulmonary hypertension of the newborn (PPHN)" and that "[t]he recommended dose by the FDA for the treatment of neonatal hypoxic respiratory failure is 20 ppm." *Id*. at 3. Bernasconi also states that

> PPHN is a syndrome associated with diverse neonatal cardiopulmonary disorders, which are characterised by a high pulmonary vascular resistance with right to left shunt of deoxygenated blood across the ductus arteriosus and/or the foramen ovale. The role of echocardiography to confirm the diagnosis and conduct therapy is therefore essential. Echocardiography also excludes structural congenital heart disease, which would contraindicate the use of iNO.

Id. at 8.

Bernasconi also teaches that iNO may lead to pulmonary edema in patients with LVD and, thus, emphasizes a need for "careful observation and intensive monitoring during [nitric oxide] inhalation" in patients with LVD. *Id.*

2. INOmax Label (Ex. 1014)

INOmax label contains information provided to medical providers (Ex. 1014 at i) regarding approved iNO uses and contraindications (*id.* at 4, 6). In particular, the reference states that "INOmax, in conjunction with ventilatory support and other appropriate agents, is indicated for the treatment of term and near-term (>34 weeks) neonates with hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension, where it improves oxygenation and reduces the need for extracorporeal membrane oxygenation." *Id.* at 4. INOmax label warns that the drug "should not be used in the treatment of neonates known to be dependent on right-to-left shunting of blood." *Id.* INOmax label states

that for "Pediatric Use[, n]itric oxide for inhalation has been studied in a neonatal population" (*id.* at 5) and recommends a dose of 20 ppm iNO for neonatal patients with hypoxic respiratory failure (*id.* at 6).

3. Loh (Ex. 1006)

Loh describes a study of the hemodynamic effects of a ten-minute inhalation of nitric oxide (80 ppm) in nineteen adult patients with moderate to severe heart failure due to LVD. Ex. 1006, 2780. Loh further describes measuring the PCWP in the patients studied. *Id.* at 2781.

4. Goyal (Ex. 1007)

Goyal describes a study of the efficacy of inhaled nitroglycerin in reducing pulmonary arterial hypertension in children with congenital heart disease. Ex. 1007, Abstract. During the study, PCWP was measured for all of the patients before and after treatment with inhaled nitroglycerin. *Id.* at 209.

5. Analysis

Petitioner argues that the combination of Bernasconi, INOmax label, Loh, and Goyal teaches or suggests each limitation of the independent claims in the '966 patent, the '284 patent, and the '163 patent. Petitioner also argues that the combination of Bernasconi, Loh, and Goyal teaches or suggests each limitation of independent claims 1, 9, 34, and 37 of the '741 patent. In particular, regarding the exclusion limitations of the claims, Petitioner asserts that Bernasconi discloses that patients with LVD treated with inhaled nitric oxide are at risk of pulmonary edema. -522 Pet. 27 (regarding independent claims 1 and 6 of the '966 patent) (citing Ex. 1004, 8; Ex. 1002 ¶ 38); *see also id.* at 32 (regarding independent claims 13 and 22 of the '966 patent). According to Petitioner, a person of ordinary skill in the art "would have known not to harm patients by administering iNO to

patients at particular risk of developing pulmonary edema." *Id.* at 27 (citing Ex. 1004, 8; Ex. 1002 ¶¶ 24, 34, 38). Petitioner then concludes that a person of ordinary skill in the art "would have known to exclude certain neonates identified as having LVD from iNO treatment." *Id.* (citing Ex. 1004, 8; Ex. 1002 ¶ 38). Petitioner makes the same arguments with respect to the independent claims of the '284 patent and the '163 patent, and independent claims 1, 9, 34, and 37 of the '741 patent. *See* -524 Pet. 25, 30; -525 Pet 23, 28; -526 Pet. 13–25.

We are not persuaded by Petitioner's argument. Bernasconi teaches that there are "several reports of the negative effects of inhaled NO in patients with left ventricular dysfunction." Ex. 1004, 8. Those negative effects include the risk of pulmonary edema. *Id.* But the Specification acknowledges that the risk of pulmonary edema was already known, stating "pulmonary edema has previously been reported with the use of iNO in patients with LVD." Ex. 1001, 13:4–5. And, as Patent Owner notes, despite this knowledge in the art, Bernasconi does not conclude that patients should be excluded from inhaled nitric oxide treatment as a result of a determination that a patient has LVD, as required by the claims. *See* -522 Prelim. Resp. 41. Instead, Bernasconi merely cautions for the "need for careful observation and intensive monitoring *during* NO inhalation in patients with left ventricular failure, if left ventricular afterload is not lowered concomitantly." *See* Ex. 1004, 8 (emphasis added). Thus, contrary to the claim language, Bernasconi teaches that iNO treatment may be given to patients with LVD, as long as those patients are monitored carefully during treatment.

We are also not persuaded that Petitioner has shown sufficiently that the teachings of Bernasconi would suggest to a person of ordinary skill in

the art that *children* with LVD are at an increased risk of pulmonary edema and should, therefore, be excluded from treatment with inhaled nitric oxide. Petitioner's declarant, Dr. Beghetti—who is an author of Bernasconi—states that "the discussion of adverse effects of iNO on patients with LVD is applicable to all patients, including the '[n]eonates with hypoxaemic respiratory failure' addressed in the 'Inhaled nitric oxide applications' section of *Bernasconi*." Ex. 1002 ¶ 36. Dr. Beghetti continues, stating that "the risk of pulmonary oedema resulting from iNO therapy in patients with LVD is a risk in neonates and non-neonates alike." *Id.* Finally, Dr. Beghetti concludes that after reading Bernasconi, evaluating the patient, and weighing the therapeutic benefits of iNO, "one skilled in the art would have understood that certain patients who have left ventricular dysfunction would be at risk of pulmonary oedema, even if not dependent on right-to-left shunting of blood, and should not be treated with inhaled NO." *Id.* ¶ 38.

Dr. Beghetti, however, does not provide any objective support for his opinion that such patients "should not be treated with inhaled NO" (*id.*), particularly when Bernasconi itself taught that treatment with iNO was acceptable, as long as the patient is carefully monitored. We, therefore, do not give persuasive weight to Dr. Beghetti's unsupported opinion. *See* 37 C.F.R. § 42.65(a) (stating opinion testimony that does not disclose underlying facts or data "is entitled to little or no weight"); *Ashland Oil, Inc. v. Delta Resins & Refractories, Inc.*, 776 F.2d 281, 294 (Fed. Cir. 1985) (finding a lack of objective support for expert opinion "may render the testimony of little probative value in a validity determination").

Moreover, Dr. Beghetti provides no persuasive support for his opinion that a person of ordinary skill in the art reading Bernasconi would understand that the risk of pulmonary edema from iNO therapy in patients

with LVD "is a risk in neonates and non-neonates alike." Ex. 1002 ¶ 36. In contrast, Patent Owner provides a number of prior art references that explain that LVD in adults is different than LVD in children, and that state "children are not simply little adults." -522 Prelim. Resp. 30 (citing Ex. 2004, 2; Ex. 1017, 117; Ex. 2009, 1215; Ex. 2010, 5, 8; Ex. 2011, 544; Ex. 2006, 2).

The INOT22 study also provides compelling evidence that the claims are not obvious. As noted above, the Specification acknowledges that it was known in the art that iNO treatment in patients with LVD may cause pulmonary edema. Ex. 1001, 13:6–7. Nevertheless, those patients were not excluded from the original protocol of the study, which, according to the Specification, "was the largest and most rigorous pharmacodynamics study of iNO conducted to date." *Id.* at 13:44–46. We find persuasive Patent Owner's argument and evidence that, if it were obvious to a person of ordinary skill in the art to exclude children with LVD from treatment with iNO, the experts in the field who designed the study—including the named author of the Macrae reference relied on by Petitioner—would have excluded those children from the original protocol. -522 Prelim. Resp. 45, 34.

Finally, during prosecution of the involved patents, the applicants made many of the same arguments that Patent Owner makes in its Preliminary Responses. That is, the applicants argued that studies on adults with LVD, like that described in Loh, could not be extrapolated to results in children, because "LVD in children or neonates is 'drastically different' than LVD in adults." -522 Prelim. Resp. 15–17 (citation omitted). The applicants also argued that the fact that children with LVD were not excluded from the original protocol of the INOT22 study is evidence of nonobviousness. *Id.* at 48. Petitioner, however, does not address any of

these arguments in its Petition, despite including the file history as an exhibit. *See* Ex. 1052. Given the Examiner found these arguments persuasive and allowed the claims, we agree with Patent Owner that Petitioner and its declarant should have addressed these arguments in the Petitions to show a reasonable likelihood of success on the merits.

Accordingly, we find that Petitioner has failed to show sufficiently that the cited art teaches or suggests the exclusion limitation of the claims. Thus, after considering the parties' arguments and evidence, we are not persuaded that Petitioner has established a reasonable likelihood of success that it would prevail in showing any of the claims of the '966 patent, the '284 patent, and the '163 patent are unpatentable as obvious over Bernasconi, INOmax label, Loh, and Goyal, or that claims 1–23, 31, 32, and 34–44 of the '741 patent are unpatentable as obvious over Bernasconi, Loh, and Goyal.

C. Obviousness of the '966 Patent, the '284 Patent, and the '163 Patent Claims over Ichinose, Neonatal Group, Macrae, Loh, Goyal, and Germann

Relying on the testimony of Dr. Beghetti, Petitioner also asserts that each of the independent claims of the '966 patent, the '284 patent, and the '163 patent is unpatentable as obvious over Ichinose, Neonatal Group, Macrae, Loh, Goyal, and Germann. -522 Pet. 41–53. Patent Owner opposes Petitioner's assertion. -522 Prelim. Resp. 53–55. We determine, on the current record, that Petitioner has not established a reasonable likelihood that it would prevail in showing the cited references render any of those challenged claims obvious.

1. Ichinose (Ex. 1009)

Ichinose is a review article disclosing the uses and therapeutic potential of inhaled nitric oxide. Ex. 1009, 3106. Ichinose discusses the

approval of iNO for the treatment of newborns with hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension. *Id.* at 3107–08. Ichinose also states that, although early studies of inhaled nitric oxide to treat pulmonary hypertension used concentrations of 5 to 80 ppm, it has since been recognized that concentrations greater than 20 ppm provide little additional therapeutic benefit in most patients. *Id.* at 3106. Ichinose further states that inhalation of low levels of nitric oxide appears to be safe, but that "it is important to be aware of the possibility that inhaled NO can produce pulmonary vasodilation and may overwhelm a failing [left ventrical], thereby producing pulmonary edema." *Id.* at 3109.

2. Neonatal Group (Ex. 1011)

Neonatal Group describes the results of a randomized, multicenter study to determine whether inhaled nitric oxide would reduce mortality or the initiation of extracorporeal membrane oxygenation in infants with hypoxic respiratory failure. Ex. 1011, Abstract. The study found that nitric oxide therapy reduced the use of extracorporeal membrane oxygenation, but had no apparent effect on mortality in critically ill infants with hypoxic respiratory failure. *Id.*

3. Macrae (Ex. 1008)

Macrae discusses the use of inhaled nitric oxide in neonates and children with cardiorespiratory failure. Ex. 1008, Abstract. Macrae notes that studies of inhaled nitric oxide in term or near-term babies have used echocardiography to exclude patients with congenital heart disease as a cause of hypoxemia. *Id.* at 373–74. For example, Macrae states that inhaled nitric oxide may be harmful to babies with severe LVD with right-to-left ductal shunting. *Id.* at 374.

4. Germann (Ex. 1010)

Germann discloses the use of inhaled nitric oxide to treat acute respiratory failure and pulmonary hypertension in adults. Ex. 1010, Abstract. Germann also provides expert recommendations for the use of inhaled nitric oxide in adults. *Id.* For example, for patients with chronic left ventricular failure, Germann states that some studies report sudden development of pulmonary edema in patients with severe congestive heart failure who were treated with inhaled nitric oxide. *Id.* at 1033. Germann further states that inhaled nitric oxide may be dangerous in patients with LVD. *Id.*

5. Analysis

Petitioner asserts that the combination of Ichinose, Neonatal Group, Macrae, Loh, Goyal, and Germann teaches or suggests each limitation of each of the independent claims of the '966 patent, the '284 patent, and the '163 patent. In particular, for the exclusion limitation of the independent claims of the '966 patent, Petitioner asserts that a person of ordinary skill in the art would have known that "all patients with LVD, ***whether or not*** they depended on right-to-left shunting, were at risk of pulmonary edema if treated with iNO." -522 Pet. 48 (citing Ex. 1009, 3109; Ex. 1002 ¶¶ 61, 67). Petitioner further argues that Ichinose discloses that patients with LVD treated with iNO are at risk of pulmonary edema. *Id.* (citing Ex. 1009, 3109). Moreover, Petitioner asserts that Germann discloses that "treating patients with LVD with iNO may be dangerous," because Germann states that "[i]n the presence of left heart dysfunction it is increasingly recognised that iNO testing should be performed only after optimising heart failure therapy immediately prior to testing." *Id.* at 48–49 (citing Ex. 1010, 1033; Ex. 1002 ¶ 67). Petitioner concludes that a person of ordinary skill in the art

reading Ichinose and Germann would have understood that patients with LVD were at risk of pulmonary edema upon treatment with iNO and "would have evaluated the risks associated with iNO treatment and excluded the patients from iNO treatment." *Id.* at 49 (citing Ex. 1002 ¶¶ 63, 65, 67, 72; Ex. 1009, 3109; Ex. 1010, 1033). Petitioner makes the same arguments with respect to the '284 and '163 patents. -524 Pet. 46–47, 50–51; -525 Pet. 40–41, 44–45.

Patent Owner asserts that both Ichinose and Germann relate to patient populations that are distinct from the claimed excluded group, and Petitioner does not explain why the teachings of those references would be applied by a person of ordinary skill in the art to the claimed excluded group. -522 Prelim. Resp. 54. For example, Patent Owner notes that Germann relates to inhaled nitric oxide therapy in adults, not children. *Id.* at 55; *see* Ex. 1010, Title, Abstract.

Patent Owner also notes that the reference cited by Ichinose as support for the risk of pulmonary edema, Beghetti (1997),[16] was a letter to the editor in response to a case study reported in Henrichsen.[17] Ex. 2004, 844. Henrichsen describes a baby with PPHN and LVD who developed systemic hypotension after exposure to inhaled nitric oxide. Ex. 1030, 183. That baby, however, was dependent on right-to-left shunting of blood, a condition which is expressly excluded from each of the claims. *See id.*; *see, e.g.*, Ex. 1001, claim 1 (performing echocardiography to identify a child in need of iNO "wherein the child is not dependent on right-to-left shunting of

[16] M. Beghetti et al., Letter to the Editor, *Inhaled Nitric Oxide Can Cause Severe Systemic Hypotension,* 130 J. PEDIATR. 844 (1997) (Ex. 2004).

[17] T. Henrichsen et al., Letter to the Editor, *Inhaled Nitric Oxide Can Cause Severe Systemic Hypotension,* 129 J. PEDIATR. 183 (1996) (Ex. 1030).

blood"). Moreover, when specifically discussing the treatment of newborns, Ichinose states "[l]arge clinical trials have demonstrated that NO inhalation is safe in the hypoxemic term newborn." Ex. 1009, 3108.

After considering both parties' arguments and evidence, we are not persuaded that Petitioner has shown sufficiently that the combination of Ichinose and Germann teaches or suggests the exclusion limitation of the claims, as Petitioner asserts. As explained above, we are not persuaded that Petitioner has shown sufficiently that a person of ordinary skill in the art would reasonably expect that children with LVD would be at risk of SAEs like pulmonary edema from iNO treatment. For example, we are not persuaded that a person of ordinary skill in the art would apply studies regarding iNO treatment in adults to treatment in children. We are, therefore, not persuaded that a person of ordinary skill in the art would apply Germann's teachings for adult iNO treatment to the treatment of children. Similarly, we are not persuaded that a person of ordinary skill in the art would look to Ichinose and its observations with respect to a neonate dependent on right-to-left shunting of blood when such patients are excluded from the claimed methods. Finally, as explained above, we are persuaded by the fact that the experts in the field designing the INOT22 study did not exclude children with LVD from the original protocol.

Accordingly, after considering both parties' arguments and evidence, we are not persuaded that Petitioner has shown a reasonable likelihood that it would prevail in showing that any of the claims of the '966 patent, the '284 patent, and the '163 patent are unpatentable as obvious over Ichinose, Neonatal Group, Macrae, Loh, Goyal, and Germann.

D. Obviousness of Claims 1–23, 31, 32, and 34–44 of the '741 Patent over Ichinose, Neonatal Group, Macrae, Loh, Goyal, and Germann

Petitioner asserts that claims 1–23, 31, 32, and 34–44 of the '741 patent are unpatentable over Ichinose, Neonatal Group, Macrae, Loh, Goyal, and Germann. -526 Pet. 39–54. Regarding the exclusion limitations of independent claims 1, 9, 34, and 37, Petitioner argues that Ichinose discloses that patients with LVD treated with iNO are at risk of pulmonary edema, and that Loh discloses that patients with LVD show an increased wedge pressure upon iNO treatment. *Id.* at 46 (citing Ex. 1009, 3109; Ex. 1006, 2780–81, Table 1). Petitioner further argues that because patients with LVD were at risk of increased wedge pressure and pulmonary edema from iNO treatment, a person of ordinary skill in the art reading Ichinose and Loh "would have considered the benefits and risks of treating such patients with iNO and would have excluded such patients from or discontinued iNO treatment if the risks outweighed the benefits." *Id.*

Patent Owner asserts substantially the same arguments regarding Ichinose that it set forth with respect to the claims of the other involved patents. That is, it argues that Ichinose relates to a neonate dependent on right-to-left shunting of blood, which is "excluded from the '741 claims." -526 Prelim. Resp. 56. Patent Owner also argues that Loh, which was considered by the Examiner during prosecution, is directed to adult patients and has nothing to do with children who have LVD. *Id.* at 43 (citing Ex. 1006, 2780).

After considering both parties' arguments and evidence, we are not persuaded that Petitioner has shown sufficiently that the cited prior art teaches or suggests the exclusion limitations of the claims. As an initial matter, we note that the '741 claims do not expressly exclude children

dependent on right-to-left shunting of blood, as Patent Owner asserts. Regardless, we find persuasive Patent Owner's argument that Petitioner has failed to establish why a person of ordinary skill in the art would apply Loh's teachings relating to adults to the treatment of children. We also find persuasive Patent Owner's argument that the INOT22 study is evidence of nonobviousness, as explained above. Because Petitioner failed to address persuasively either of these arguments—despite the fact that both were raised during prosecution—we determine that Petitioner has not established a reasonable likelihood that it would prevail in showing that claims 1–23, 31, 32, and 34–44 of the '741 patent are unpatentable over Ichinose, Neonatal Group, Macrae, Loh, Goyal, and Germann.

E. Obviousness of Claims 24–30 and 33 of the '741 Patent over Bernasconi, INOmax Label, Loh, Juliana, and Goyal

Petitioner asserts that claims 24–27, 29, 30, and 33 of the '741 patent are unpatentable over Bernasconi, INOmax label, Loh, Juliana, and Goyal. -526 Pet. 54–60. Petitioner further asserts that claim 28, which depends from independent claim 24, is unpatentable over Bernasconi, INOmax label, Loh, Juliana, Macrae, and Goyal. *Id.* at 60. We determine that Petitioner has not established a reasonable likelihood that it would prevail on its assertions.

1. Juliana (Ex. 1010)

Juliana describes a case of a full-term neonate with severe PPHN. Ex. 1010, Abstract. Cardiac ultrasound confirmed a right-to-left shunt through an open arterial duct. *Id.* at 627. The patient was not treated with inhaled nitric oxide because of the high cost of the treatment, but was treated successfully with one dose of sildenafil. *Id.*

2. Analysis

As explained above, we interpret steps (d) and (e) of claim 24 as equivalent to the exclusion limitations of the other challenged claims. For the step of "determining that a second patient . . . has pre-existing left ventricular dysfunction, so is at particular risk of increased PCWP leading to pulmonary edema upon treatment with inhaled nitric oxide" of claim 24(d), Petitioner relies on its arguments with respect claim 1(c). -526 Pet. 34. That is, Petitioner argues that Bernasconi discloses that patients with LVD are at risk of pulmonary edema upon treatment with iNO. *Id.* at 20. Petitioner also argues that Loh discloses that patients with LVD have an increased wedge pressure upon iNO treatment, and that Goyal confirms that it was well known that wedge pressure could be measured in infants. *Id.* at 20–21. For step (e), "administering a second treatment regimen . . . wherein the second treatment regimen does not comprise either (i) administration of inhaled nitric oxide for 14 days or (ii) administration of inhaled nitric oxide until the second patient's hypoxia has resolved," Petitioner relies on Juliana's disclosure that neonates with PPN can be treated with sildenafil instead of inhaled nitric oxide. *Id.* at 34 (citing Ex. 1032, Abstract, 627; Ex. 1002 ¶ 53). Petitioner then concludes that a person of ordinary skill in the art reading Juliana "would have understood to administer a treatment other than iNO, *i.e.*, sildenafil." *Id.* at 34–35.

For the same reasons stated above, we are not persuaded that Petitioner has shown sufficiently that a person of ordinary skill in the art reading Bernasconi and Loh would reasonably expect neonates with LVD to be "at particular risk of increased PCWP leading to pulmonary edema upon treatment with inhaled nitric oxide," as required by claim 24(d). Accordingly, we determine that Petitioner has not established a reasonable

likelihood that it would prevail in showing that claims 24–30 and 33 of the '741 patent are unpatentable over the cited references.

III. CONCLUSION

We conclude that Petitioner has not demonstrated a reasonable likelihood of prevailing on its assertions that claims 1–29 the '966 patent; claims 1–30 of the '284 patent; claims 1–25 of the '163 patent; and claims 1–44 of the '741 patent are unpatentable as obvious.

IV. ORDER

In consideration of the foregoing, it is hereby ordered that the Petitions in IPR2015-00522, IPR2015-00524, IPR2015-00525, and IPR2015-00526 are *denied*.

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EXHIBIT U

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

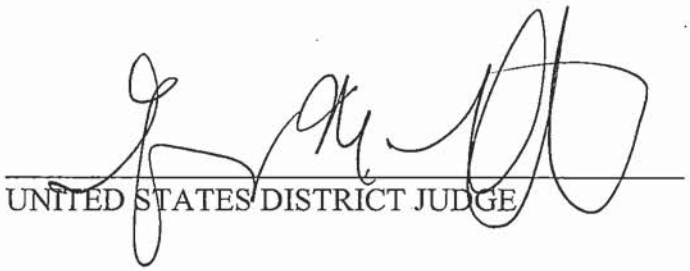
VANDA PHARMACEUTICALS, ET AL.	
Plaintiffs,	Civil Action No. 13-1973-GMS
v.	
	Civil Action No. 14-757-GMS
ROXANE LABORATORIES, INC.,	
Defendant.	

ORDER

At Wilmington, this 30th day of December 2015, having considered the defendant's letter of request to file a motion for summary judgment asserting invalidity of claims 1-9, 11-13, and 16 of United States Patent No. 8,586,610 (the "'610 patent") for lack of patentable subject matter under 35 U.S.C. § 101 (D.I. 133), and Vanda's response thereto (D.I. 140);

IT IS HEREBY ORDERED that the letter request to file a motion for summary judgment (D.I. 132) is DENIED. There are disputes of material facts which raise genuine issues for trial.[1]

[1] The court finds, based on its review of the parties' submissions and the cited record, that material facts remain in dispute as to Roxane's claim of invalidity under 35 U.S.C. § 101. In order to meet the standard for summary judgment, Roxane must establish the absence of a genuine dispute of material facts. *Celotex Corp. v. Catrett,* 477 U.S. 317, 323-24 (1986). Patentability under Section 101 is a question of law based on underlying facts. *In re Cominskey,* 554 F.3d 967, 975 (Fed. Cir. 2009). Roxane argues that the asserted claims of the '610 are patent ineligible because they do nothing more than combine a law of nature with routine and conventional steps. *See Mayo Collaborative Services v. Prometheus Laboratories, Inc.,* 132 S. Ct. 1289, 1294 (2012). (D.I. 133 at 2.) Vanda disputes (1) that there is a law of nature here, (2) that the steps are routine and conventional, and (3) that these claims are analogous to those at issue in *Mayo.* (D.I. 140 at 1). Vanda will offer expert testimony in support of each of these assertions. *Id.* at 5. Moreover, Vanda points out that the PTO explicitly considered the '610 patent in light of *Mayo* and upheld the patentability of the claims. *Id.* at 1. Thus, the court concludes that these issues of material fact are properly determined at trial.



UNITED STATES DISTRICT JUDGE

EXHIBIT V

US008795741B2

(12) **United States Patent**
Baldassarre

(10) **Patent No.: US 8,795,741 B2**
(45) **Date of Patent: *Aug. 5, 2014**

(54) **METHODS FOR TREATING PATIENTS WHO ARE CANDIDATES FOR INHALED NITRIC OXIDE TREATMENT**

(71) Applicant: **INO Therapeutics LLC**, Hampton, NJ (US)

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(73) Assignee: **INO Therapeutics LLC**, Hampton, NJ (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **13/683,417**

(22) Filed: **Nov. 21, 2012**

(65) **Prior Publication Data**

US 2013/0078321 A1 Mar. 28, 2013

Related U.S. Application Data

(63) Continuation of application No. 12/820,866, filed on Jun. 22, 2010, now abandoned, which is a continuation of application No. 12/494,598, filed on Jun. 30, 2009, now abandoned, application No. 13/683,417, which is a continuation of application No. 13/651,660, filed on Oct. 15, 2012, which is a continuation of application No. 12/821,041, filed on Jun. 22, 2010, now Pat. No. 8,293,284, which is a continuation of application No. 12/494,598, filed on Jun. 30, 2009, now abandoned.

(51) **Int. Cl.**

A61B 5/02	(2006.01)
A01N 59/00	(2006.01)
A61K 33/00	(2006.01)
C01B 21/24	(2006.01)
A61M 16/12	(2006.01)
A61B 8/08	(2006.01)
A61K 45/06	(2006.01)
G06Q 99/00	(2006.01)
A61K 31/21	(2006.01)
A61M 16/00	(2006.01)

(52) **U.S. Cl.**

CPC ***A61K 33/00*** (2013.01); ***A61M 16/12*** (2013.01); ***A61B 8/48*** (2013.01); ***A61K 45/06*** (2013.01); ***G06Q 99/00*** (2013.01); ***A61K 31/21*** (2013.01)

USPC **424/718**; 128/200.24; 423/405; 600/483; 600/484; 600/485

(58) **Field of Classification Search**

None

See application file for complete search history.

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(57) **ABSTRACT**

Disclosed are methods of reducing the risk that a medical treatment comprising inhalation of nitric oxide gas will induce an increase in pulmonary capillary wedge pressure in the patient, leading to pulmonary edema.

44 Claims, No Drawings

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

CROSS REFERENCE TO RELATED APPLICATIONS

This application is a continuation of U.S. application Ser. No. 12/820,866, filed Jun. 22, 2010, which is a continuation of U.S. Ser. No. 12/494,598, filed Jun. 30, 2009, and now abandoned. This application is also a continuation of U.S. Ser. No. 13/651,660, filed Oct. 15, 2012, which is a continuation of U.S. application Ser. No. 12/821,041 (now U.S. Pat. No. 8,293,284), filed Jun. 22, 2010, which is a continuation of U.S. application Ser. No. 12/494,598, filed Jun. 30, 2009, and now abandoned.

BACKGROUND OF THE INVENTION

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.

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 R G et al., 1983, Acute Hemodynamic Effects of Nitroglycerin in Pulmonary Hypertension, *American College of Physicians* 99:9-13; Ajami G H 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 J J 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 J W 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

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.

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.

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.

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.

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.

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.

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.

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.

In an exemplary embodiment of the method, the patients having pre-existing LVD demonstrate a PCWP≥20 mm Hg.

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

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.

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

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

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.

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 $u \cdot m^2$; congenital heart disease with pulmonary hypertension repaired and unrepaired characterized by PAPm>25 mm Hg at rest and PVRI>3 $u \cdot m^2$; cardiomyopathy characterized by PAPm>25 mm Hg at rest and PVRI>3 $u \cdot m^2$; or the patient is scheduled to undergo right heart catheterization to assess pulmonary vasoreactivity by acute pulmonary vasodilatation testing.

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

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.

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 U.S. Pat. Nos. 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; U.S. patent application Ser. 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.

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.

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

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

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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 L J, Kerr K M, Pulmonary Hypertension, in *Critical Care Medicine: Principles of Diagnosis and Management in the Adult,* 2*d Ed*., Parillo J E, Dellinger R P (eds.), Mosby, Inc. 2001, pp. 900-09 at 906; Kinsella J P, Abman S H, The Role of Inhaled Nitric Oxide in Persistent Pulmonary Hypertension of the Newborn, in *Acute Respiratory Care of the Neonate: A Self-Study Course,* 2*d Ed*., Askin D F (ed.), NICU Ink Book Publishers, 1997, pp. 369-378 at 372-73).

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.

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

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).

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

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

NINOS Study.

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

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

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.

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 AE of treatment on the need for re-hospitalization, 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, per ventricular 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. 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%)

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.

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

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).

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.

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.

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.

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 · 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)

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)

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

TABLE 6-continued

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)
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)

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.

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.

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.

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.

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

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 C S et al., 1996, Inhaled Nitric Oxide in Cardiac Failure: Vascular Versus Ventricular Effects, *J Cardiovascular Pharmacology* 27:80-85; Bocchi E A et al., 1994, Inhaled Nitric Oxide Leading to Pulmonary Edema in Stable Severe Heart Failure, *Am J Cardiology* 74:70-72; and, Semigran M J et al., 1994, Hemodynamic Effects of Inhaled Nitric Oxide in Heart Failure, *J Am Coll Cardiology* 24:982-988).

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 E A et al., 1994; Semigran M J et al., 1994).

In the INOT22 study, 10 of the total 134 patients had a baseline PCWP>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.

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.

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.

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 C J 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.

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

We claim:

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

(a) 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;

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

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

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

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

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

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

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

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

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

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

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

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

(a) 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;

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

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

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

(e) excluding the second patient from treatment with inhaled nitric oxide based on the determination in (c), or, despite the second patient's ongoing need for inhaled nitric oxide treatment for hypoxic respiratory failure, discontinuing the second patient's treatment with inhaled nitric oxide after it was begun, the discontinuation being in view of the determination in (c).

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

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

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

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

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

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

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

17. The method of claim 9, wherein

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

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

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

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

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

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

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

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

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

(a) 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;

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

(c) administering a first treatment regimen to the first patient, wherein the first treatment regimen comprises administration of 20 ppm inhaled nitric oxide for 14 days or until the first patient's hypoxia has resolved;

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

(e) administering a second treatment regimen to the second patient, wherein the second treatment regimen does not comprise either (i) administration of inhaled nitric oxide for 14 days or (ii) administration of inhaled nitric oxide until the second patient's hypoxia has resolved.

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

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

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

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

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

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

31. The method of claim 1, wherein identifying the plurality of term or near-term neonatal patients who have hypoxic respiratory failure and are candidates for 20 ppm inhaled nitric oxide treatment comprises performing at least one diagnostic process.

32. The method of claim 9, wherein identifying the plurality of term or near-term neonatal patients who have hypoxic respiratory failure and are candidates for 20 ppm inhaled nitric oxide treatment comprises performing at least one diagnostic process.

33. The method of claim 24, wherein identifying the plurality of term or near-term neonatal patients who have hypoxic respiratory failure and are candidates for 20 ppm inhaled nitric oxide treatment comprises performing at least one diagnostic process.

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

(a) identifying a plurality of patients who are children with a condition that makes them candidates for 20 ppm inhaled nitric oxide treatment;

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

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

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

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

35. The method of claim 34, wherein the second patient is determined to be at particular risk not only of increased PCWP leading to pulmonary edema, but also of other serious adverse events, upon treatment with inhaled nitric oxide, and the second patient is excluded from inhaled nitric oxide treatment based on the determination that the second patient has left ventricular dysfunction and so is at particular risk not only of increased PCWP leading to pulmonary edema, but also other serious adverse events, upon treatment with inhaled nitric oxide.

36. The method of claim 34, wherein the left ventricular dysfunction of the second patient is attributable to congenital heart disease.

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

(a) identifying a plurality of patients who are children with a condition that makes them candidates for 20 ppm inhaled nitric oxide treatment;

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

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

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

(e) excluding the second patient from treatment with inhaled nitric oxide based on the determination in (c), or, despite the second patient's ongoing need for inhaled nitric oxide treatment for hypoxic respiratory failure, discontinuing the second patient's treatment with inhaled nitric oxide after it was begun, the discontinuation being in view of the determination in (c).

38. The method of claim 37, wherein the discontinuation is in view of both the determination in (c) and the second patient's experiencing an adverse event upon treatment with inhaled nitric oxide.

39. The method of claim 38, wherein the adverse event comprises pulmonary edema.

40. The method of claim 38, wherein the adverse event comprises at least one of increased PCWP, systemic hypotension, bradycardia, or cardiac arrest.

41. The method of claim 37, wherein the left ventricular dysfunction of the second patient is attributable to congenital heart disease.

42. The method of claim 37, wherein

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

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

43. The method of claim 42, wherein the other serious adverse events comprise one or more of increased PCWP, systemic hypotension, bradycardia, or cardiac arrest.

44. The method of claim 42, wherein the discontinuation is in view of:

the determination in (c), the determination that the second patient is also at risk of other serious adverse events, and the second patient's experiencing an adverse event upon treatment with inhaled nitric oxide.

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