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(54) **METHODS FOR TREATING PATIENTS WHO ARE CANDIDATES FOR INHALED NITRIC OXIDE TREATMENT**

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(56) **References Cited**

U.S. PATENT DOCUMENTS

5,558,083 A 9/1996 Bathe et al.
5,651,358 A 7/1997 Briend et al.
5,873,359 A 2/1999 Zapol et al.
6,063,407 A 5/2000 Zapol et al.
6,142,147 A 11/2000 Head et al.
6,601,580 B1 8/2003 Bloch et al.
7,557,087 B2 7/2009 Rothbard et al.
2002/0185126 A1 12/2002 Krebs
2003/0131848 A1 7/2003 Stenzler
2004/0106954 A1 6/2004 Whitehurst et al.
2009/0018136 A1 1/2009 Oppenheimer et al.
2009/0029371 A1 1/2009 Elliott
2009/0149541 A1 6/2009 Stark et al.
2009/0176772 A1 7/2009 Blackburn et al.

FOREIGN PATENT DOCUMENTS

EP 1682672 7/2006
WO WO2005004884 1/2005
WO WO2006127907 11/2006
WO WO2010019540 2/2010

OTHER PUBLICATIONS

Rosales et al. (Pediatric Cardiology, 1999, 20:224-226).
Kieler-Jensen et al., "Inhaled nitric oxide in the evaluation of heart transplant candidates with elevated pulmonary vascular resistance", J. Heart Lung Transplant, vol. 13, pp. 366-375 (1994).
Kinsella et al., "Inhaled nitric oxide in premature neonates with severe hypoxaemic respiratory failure: a randomised controlled trial," The Lancet, vol. 354, pp. 1061-1065 (1999).
Konduri et al., "A Randomized Trial of Early Versus Standard Inhaled Nitric Oxide Therapy in Term and Near-Term Newborn Infants with Hypoxic Respiratory Failure," Pediatrics, vol. 113 No. 3, pp. 559-564 (2004).
Krasuski et al., "Inhaled Nitric Oxide Selectively Dilates Pulmonary Vasculature in Adult Patients With Pulmonary Hypertension, Irrespective of Etiology," Journal of the American College of Cardiology (JACC), vol. 36, No. 7, pp. 2204-2211 (2000).
Krohn, "Effect of inhaled nitric oxide on left ventricular and pulmonary vascular function," The Journal of Thoracic and Cardiovascular Surgery, vol. 117(1), pp. 195-196 (1999).
Kulik, "Inhaled nitric oxide in the management of congenital heart disease," Current Opinion in Cardiology, vol. 11, pp. 75-80 (1996).
Lavigne et al., "Cardiovascular Outcomes of Pediatric Seroreverters Perinatally Exposed to HAART," Cardiovascular Toxicology, vol. 4, pp. 187-197 (2004).
Letter of Acceptance for AU 2010202422, dated Oct. 7, 2010.
Letter of acceptance of AU application 2009202685, dated Aug. 10, 2010, 3 pages.
Lipschultz, "The effect of dexrazoxane on myocardial injury in doxorubicin-treated children with acute lymphoblastic leukemia," New England Journal of Medicine, vol. 351, pp. 145-153 (2004).

(Continued)

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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 pressure in the patient, leading to pulmonary edema.

(56)

References Cited

OTHER PUBLICATIONS

- Lipshultz, "The incidence of pediatric cardiomyopathy in two regions of the United States," *New England Journal of Medicine*, Apr. 24, 2003. <<<http://www.nejm.org/doi/full/10.1056/NEJMoa021715>>>.
- Lipshultz, "Ventricular dysfunction clinical research in infants, children and adolescents," *Progress in Pediatric Cardiology*, vol. 12, pp. 1-28 (2000).
- Lipshultz, "Chronic Progressive Cardiac Dysfunction Years After Doxorubicin Therapy for Childhood Acute Lymphoblastic Leukemia," *Journal of Clinical Oncology*, vol. 23, No. 12, 8 pages (2005).
- Lipshultz, "Clinical research directions in pediatric cardiology," *Current Opinion in Pediatrics*, vol. 21, pp. 585-593 (2009).
- Lipshultz, "Establishing norms for echocardiographic measurement of cardiovascular structures and function in children," *J. Appl. Physiol.*, vol. 99, pp. 386-388 (2005).
- Lipshultz et al., "Cardiovascular status of infants and children of women infected with HIV-1 (P2C2 HIV): a cohort study," *The Lancet*, vol. 360, pp. 368-373 (2002).
- Lipshultz et al., "Cardiovascular Trials in Long-Term Survivors of Childhood Cancer," *Journal of Clinical Oncology*, vol. 22, No. 5, pp. 769-773 (2004).
- Lipshultz et al., "Long-Term Enalapril Therapy for Left Ventricular Dysfunction in Doxorubicin-Treated Survivors of Childhood Cancer," *Journal of Clinical Oncology*, vol. 20, No. 23, pp. 4517-4522 (2002).
- Lipshultz, "Frequency of clinically unsuspected myocardial injury at a children's hospital," *American Heart Journal*, vol. 151, No. 4, pp. 916-922 (2006).
- Loh et al., "Cardiovascular Effects of Inhaled Nitric Oxide in Patients with Left Ventricular Dysfunction," *Circulation*, vol. 90, pp. 2780-2785 (1994).
- Macrae et al., "Inhaled nitric oxide therapy in neonates and children: reaching a European consensus," *Intensive Care Med.*, vol. 30, pp. 372-380 (2004).
- Madriago et al., "Heart Failure in Infants and Children," *Pediatrics in Review*, vol. 31, pp. 4-12 (2010).
- Magee et al., "Comparison of Supplemental Oxygen and Nitric Oxide for Inhalation plus oxygen in the evaluation of the reactivity of the pulmonary vasculature during Acute Pulmonary Vasodilator Testing," Oct. 1, 2004-Oct. 31, 2006, Research project description, 1 page, <http://www.rbht.nhs.uk/research>.
- Malloy, "Nitric Oxide Weaning, RT: For Decision Makers in Respiratory Care," http://rtmagazine.com/issues/articles/2000-12_05.asp, 3 pages, Dec. 2000.
- Martinez et al., "Dermatological Cryosurgery in Primary Care with Dimethyl Ether Propane Spray in Comparison with Liquid Nitrogen," *Atencion Primaria*, vol. 18, No. 5, pp. 211 and 216 (1996).
- Matsumoto et al., "Effect of Inhaled Nitric Oxide on Gas Exchange in Patients with Congestive Heart Failure," *Annals of Internal Medicine*, vol. 130, No. 1, pp. 40-44 (1999).
- Meyler's Side Effects of Drugs: The International Encyclopedia of Adverse Drug Reactions and Interactions, Nitric Oxide, Fifteenth Edition, Elsevier B.V. (2006).
- Michelakis et al., "Oral Sildenafil is an Effective and Specific Pulmonary Vasodilator in Patients with Pulmonary Arterial Hypertension: Comparison with Inhaled Nitric Oxide," *Circulation* vol. 105, pp. 2398-2403 (2002).
- Miller et al., "Nutrition in Pediatric Cardiomyopathy," *Prog. Pediatr. Cardiol.* vol. 24(1), pp. 59-71 (2007).
- Mone, "Effects of Environmental Exposures on the Cardiovascular System: Prenatal Period Through Adolescence," *Pediatrics*. vol. 113, No. 4, pp. 1058-1069 (2004).
- Morales-Blanchir et al., "Clinical value of vasodilator test with inhaled nitric oxide for predicting long-term response to oral Moss et al., "Moss and Adams' Heart Disease in Infants, Children, and Adolescents," *Coarctation of the Aorta*, vol. 1, p. 991 in part (2007).
- Murray, "Angiotensin Converting Enzyme Inhibitory Peptides Derived from Food Proteins: Biochemistry, Bioactivity and Production," *Current Pharmaceutical Design*, pp. 773-791 (2007).
- Murray et al., "Nitric Oxide and Septic Vascular Dysfunction," *Anesth. Analg.* vol. 90, pp. 89-101 (2000).
- Natori et al., "Inhaled Nitric Oxide Modifies Left Ventricular Diastolic Stress in the Presence of Vasoactive Agents in Heart Failure," *Am. J. Respir. Crit. Care Med.* vol. 167, pp. 895-901 (2003).
- NIH CC: Critical Care Services, http://www.cc.nih.gov/ccmd/clinical_services.html; retrieved Mar. 10, 2011, 3 pages.
- "NIH Clinical Center 2 Critical Care Medicine Department Sample Rotations, Updated Jan. 2007" <<http://www.cc.nih.gov/ccmd/prof_opps/rotation.html>>.
- NIH Clinical Center Services, retrieved at <http://www.cc.nih.gov/ccmd/clinical_services.html>> on Aug. 18, 2010.
- NIH Clinical Center, Department Policy and Procedure Manual for the Critical Care Therapy and Respiratory Care Section; Nitric Oxide Therapy, sections 3.1-3.1.2 & 5.2.3 (2000).
- NIH Clinical Center 2 Critical Care Medicine Department Sample Rotations, Updated Jan. 2007.
- Notification of Reason for Rejection, mailed Jul. 30, 2010, from Japanese Patent Application No. 2009-157623 (cites foreign references).
- Office Action for AU 2010202422 dated Jul. 9, 2010, 3 pages.
- Office Action from AU 2009202685 dated Mar. 15, 2010.
- Office Action from AU 2010206032 dated Aug. 16, 2010 (3 pages).
- Office Action Response for AU 2009202685 to Mar. 15, 2010 OA, filed Jun. 8, 2010 (16 pages).
- Office Action Response for JP2007157623 filed on Nov. 12, 2009 (no English translation).
- Office Action Response to AU 2010202422 OA dated Jul. 9, 2010, response filed Sep. 1, 2010.
- www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidance/ucm073087.pdf, Mar. 1995.
- Notice of Abandonment in U.S. Appl. No. 12/820,866, mailed Dec. 20, 2012 (2 pages).
- Ameduri et al., Heart Failure in Children, MED-Continuing Medical Education, University of Minnesota. Jul. 29, 2009 (cited Nov. 12, 2010); available from URL: http://www.cme.umn.edu/prod/groups/med/@pub/@med/@cme/documents/content/med_content_124593.pdf.
- Konduri, "Early inhaled nitric oxide therapy for term and near-term newborn infants with hypoxic respiratory failure: neurodevelopmental follow-up," *J. Pediatr.* vol. 150(3), pp. 235-240, 240.e.1 (2007).
- Barrington et al., "Inhaled nitric oxide for respiratory failure in preterm infants (review)," *The Cochrane Collaboration*, Wiley Publishers, 3 pages (2009).
- Barst, *Pediatr.*, "Vasodilator Testing with Nitric Oxide and/or Oxygen in Pediatric Pulmonary Hypertension," *Cardiol.*, vol. 31, pp. 598-606 (2010).
- Macrae, "Drug therapy in persistent pulmonary hypertension of the newborn," *Semin. Neonatal*, vol. 2, pp. 49-58 (1997).
- Miller et al., "Guidelines for the safe administration of inhaled nitric oxide," *Archives of Disease in Childhood*, vol. 10, pp. F47-F49 (1994).
- Office Action in U.S. Appl. No. 12/494,598, mailed Aug. 13, 2010 (26 pages).
- Notice of Abandonment in U.S. Appl. No. 12/494,598, mailed Sep. 10, 2010 (2 pages).
- Office Action in U.S. Appl. No. 12/820,866, mailed Sep. 23, 2010 (26 pages).
- Lee & Hayes, Reply Amendment (Accelerated Exam-Transmittal Amendment/Reply) in U.S. Appl. No. 12/820,866 mailed Sep. 23, 2010, filed Oct. 1, 2010 (22 pages).

(56)

References Cited

OTHER PUBLICATIONS

Lee & Hayes, Reply Amendment (Accelerated Exam-Transmittal Amendment/Reply) in U.S. Appl. No. 12/820,866 mailed Nov. 2, 2010, filed Jan. 14, 2011 (12 pages).

Advisory Action in U.S. Appl. No. 12/820,866, mailed Feb. 23, 2011 (2 pages).

Lee & Hayes, Reply After Final (Accelerated Exam-Transmittal Amendment/Reply) in U.S. Appl. No. 12/820,866 mailed Sep. 23, 2010, filed Mar. 1, 2011 (9 pages).

Lee & Hayes, Reply After Final (Accelerated Exam-Transmittal Amendment/Reply) in U.S. Appl. No. 12/820,866 mailed Sep. 23, 2010, filed Mar. 1, 2011 (5 pages).

Advisory Action in U.S. Appl. No. 12/820,866, mailed Mar. 25, 2011 (3 pages).

Lee & Hayes, Reply After Final (Accelerated Exam-Transmittal Amendment/Reply) in U.S. Appl. No. 12/820,866 mailed Nov. 2, 2010, filed May 2, 2011 (9 pages).

Office Action in U.S. Appl. No. 12/820,866, mailed Jun. 8, 2011 (32 pages).

Office Action in U.S. Appl. No. 12/820,866, Aug. 24, 2011 (23 pages).

Fish & Richardson, P.C., Reply Brief in U.S. Appl. No. 12/820,866, filed Dec. 16, 2011 (21 pages).

Fish & Richardson, P.C., Supplement to Reply Brief in U.S. Appl. No. 12/820,866, filed Jan. 3, 2012 (3 pages).

Office Action in U.S. Appl. No. 12/820,980, mailed Aug. 17, 2010 (33 pages).

Lee & Hayes, Reply Amendment in U.S. Appl. No. 12/820,980, mailed Aug. 17, 2010, filed Sep. 17, 2010 (25 pages).

Office Action in U.S. Appl. No. 12/820,980, mailed Oct. 28, 2010 (23 pages).

Supplemental Office Action in U.S. Appl. No. 12/820,980, mailed Nov. 2, 2010 (4 pages).

Lee & Hayes, Reply after Final (Accelerated Exam-Transmittal Reply) in U.S. Appl. No. 12/820,980, mailed Nov. 2, 2010, filed Nov. 12, 2010 (53 pages).

Advisory Action in U.S. Appl. No. 12/820,980, mailed Nov. 29, 2010 (3 pages).

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

Office Action in U.S. Appl. No. 12/820,980, mailed Jun. 10, 2011 (29 pages).

Lee & Hayes, Amendment in Reply to Office Action in U.S. Appl. No. 12/820,980, mailed Jun. 10, 2011, filed Jul. 11, 2011 (115 pages).

Office Action in U.S. Appl. No. 12/820,980, mailed Sep. 9, 2011 (25 pages).

Notice of Abandonment in U.S. Appl. No. 12/820,980, mailed Apr. 11, 2012 (2 pages).

Office Action in U.S. Appl. No. 12/821,020, mailed Aug. 13, 2010 (24 pages).

Lee & Hayes, Response to Office Action in U.S. Appl. No. 12/821,020, mailed Aug. 13, 2010, filed Feb. 14, 2011 (18 pages).

Lee & Hayes, Supplemental Reply Amendment in U.S. Appl. No. 12/821,020, filed Apr. 12, 2011 (9 pages).

Office Action in U.S. Appl. No. 12/821,020, mailed Jun. 27, 2011 (28 pages).

Fish & Richardson, P.C., Amendment in Reply to Office Action, in U.S. Appl. No. 12/821,020, mailed Jun. 27, 2011, filed Dec. 27, 2011 (31 pages).

Office Action in U.S. Appl. No. 12/821,020, mailed Jan. 31, 2012 (23 pages).

Interview Summary in U.S. Appl. No. 12/821,020, mailed Apr. 17, 2012 (4 pages).

Fish & Richardson, P.C., Statement of Substance of Interview and Comments on Examiner's Interview Summary, in U.S. Appl. No. 12/821,020, filed Apr. 23, 2012 (8 pages).

Office Action in U.S. Appl. No. 12/821,020, mailed Jun. 15, 2012 (56 pages).

Fish & Richardson, P.C., Amendment in Reply, in U.S. Appl. No. 12/821,020, mailed Jun. 15, 2012, filed Aug. 15, 2012 (15 pages).

Office Action in U.S. Appl. No. 12/821,041, mailed Aug. 17, 2010 (32 pages).

Lee & Hayes, Reply Amendment in U.S. Appl. No. 12/821,041, mailed Aug. 17, 2010, filed Feb. 14, 2011 (28 pages).

Lee & Hayes, Supplemental Reply Amendment in U.S. Appl. No. 12/821,041, mailed Aug. 17, 2010, filed Apr. 13, 2011 (9 pages).

Office Action in U.S. Appl. No. 12/821,041, mailed Jun. 27, 2011 (35 pages).

Fish & Richardson, P.C., Amendment in Reply to Office Action in U.S. Appl. No. 12/821,041, mailed Jun. 27, 2011, filed Jan. 6, 2012 (155 pages).

Office Action in U.S. Appl. No. 12/821,041, mailed Feb. 10, 2012 (36 pages).

Fish & Richardson, P.C., in U.S. Appl. No. 12/821,041, Supplemental Amendment and Remarks, filed May 11, 2012 (32 pages).

Office Action in U.S. Appl. No. 12/821,041, mailed Jun. 19, 2012 (61 pages).

Fish & Richardson, P.C., Amendment in Reply to Office Action, in U.S. Appl. No. 12/821,041, mailed Jun. 19, 2012, filed Aug. 15, 2012 (17 pages).

Lee & Hayes Amendment in Reply to Office Action in U.S. Appl. No. 12/820,866, mailed Jun. 8, 2011, filed Jul. 8, 2011 (23 pages).

Fish & Richardson, Brief on Appeal in U.S. Appl. No. 12/820,866, filed Oct. 4, 2011 (211 pages).

Interview Summary in U.S. Appl. No. 12/821,020, mailed Jan. 25, 2012 (4 pages).

Adatia et al., "Inhaled Nitric Oxide and Hemodynamic Evaluation of Patients With Pulmonary Hypertension Before Transplantation," *Journal of the American College of Cardiology*, Elsevier, New York, NY, vol. 25, No. 7, p. 1663, Jun. 1, 1995.

Advances in Pulmonary Hypertension, vol. 7(4), pp. 1-418, Winter 2008-2009 (entire issue).

Al-Alaiyan et al., "Inhaled nitric oxide in persistent pulmonary hypertension of the newborn refractory to high-frequency ventilation," *Crit. Care*, vol. 3, No. 1, pp. 7-10 (1999).

Argenziano et al., "Inhaled Nitric Oxide is not a Myocardial Depressant in a Porcine Model of Heart Failure," *The Journal of Thoracic and Cardiovascular Surgery*, vol. 115, pp. 700-704 (1998).

Atz et al., "Combined Effects of Nitric Oxide and Oxygen During Acute Pulmonary Vasodilator Testing," *Journal of the American College of Cardiology (JACC)*, vol. 33, No. 3, pp. 813-819 (1999).

Atz et al., "Inhaled nitric oxide in the neonate with cardiac disease," *Seminars in Perinatology*, vol. 21(5), pp. 441-455 (1997).

AU 2009202685 Office Action dated Jun. 17, 2010 (3 pages).

AU 2009202685 Office Action Response dated Jul. 29, 2010, 19 pages.

Azeka et al., "Effects of Low Doses of Inhaled Nitric Oxide Combined with Oxygen for the Evaluation of Pulmonary Vascular Reactivity in Patients with Pulmonary Hypertension," *Pediatric Cardiol.*, vol. 23, pp. 20-26 (2002).

Barrington et al., "Inhaled Nitric Oxide for Preterm Infants: A Systematic Review," *Pediatrics*, vol. 120; pp. 1088-1099, DOI: 10.1542/peds (2007).

Barst et al., "Nitric Oxide in Combination with Oxygen versus Either Oxygen Alone or Nitric Oxide Alone for Acute Vasodilator Testing in Children with Pulmonary Hypertension: A Multicenter, Randomized Study," *INO Therapeutics/Ikaria, Baltimore Convention Center*, May 3, 2009, 2 pages, Abstract, downloaded Jul. 2, 2009 from http://127.0.0.1:9080/PAS09A1/view.y?nu=PAS09L1_1507.

Barst et al., "Vasodilator Testing with Nitric Oxide and/or Oxygen in Pediatric Pulmonary Hypertension," *Pediatric Cardiology*; Published online Apr. 20, 2010, 9 pages.

Beggs et al., "Cardiac Failure in Children," 17th Expert Committee on the Selection and Use of Essential Medicines, Geneva, Mar. 2009, 31 pages.

Beghetti et al., "Inhaled nitric oxide can cause severe systemic hypotension," *Journal of Pediatrics*, p. 844 (1997).

(56)

References Cited

OTHER PUBLICATIONS

Behera et al., "Nesiritide Improves Hemodynamics in Children with Dilated Cardiomyopathy: A Pilot Study," *Pediatr. Cardiol.*, vol. 30, pp. 26-34 (2009).

Bhagavan et al., "Potential role of ubiquinone (coenzyme Q10) in pediatric cardiomyopathy," *Clinical Nutrition*, vol. 24, pp. 331-338 (2005).

Bichel et al., "Successful weaning from cardiopulmonary bypass after cardiac surgery using inhaled nitric oxide", *Pediatric Anaesthesia*, vol. 7, pp. 335-339 (1997).

Bin-Nun et al., "Role of iNO in the modulation of pulmonary vascular resistance," *Journal of Perinatology*, vol. 28, pp. S84-S92 (2008).

Bland, "Pulmonary vascular dysfunction in preterm lambs with chronic lung disease," *Am J Physical Lung Cell Mol. Physiol.*, vol. 285: L76-L85 (2003).

Bloch et al., *Cardiovasc. Res.* 2007, "Inhaled NO as a therapeutic agent," vol. 75(2), pp. 339-348 (Jul. 15, 2007).

Bocchi et al., "Inhaled Nitric Oxide Leading to Pulmonary Edema in Stable Severe Heart Failure," *The American Journal of Cardiology*, vol. 74, pp. 70-72 (1994).

Bolooki, *Clinical Application of the Intra-Aortic Balloon Pump*, 3rd Ed., pp. 252-253 (1998).

Branson, "Inhaled Nitric Oxide in Adults," *The Science Journal of the American Association for Respiratory Care 1997 Open Forum Abstracts*, Dec. 7, 1997, 2 pages, retrieved at <<<http://www.rcjournal.com/abstracts/1997?id=A00000929>>> on Dec. 22, 2010.

Braunwald, *Heart Failure*, chapter 233 of *Harrison's Principles of Internal Medicine*, 14th Edition, pp. 1287-1291 and 1360 (1998).

Bublik et al., "Pediatric cardiomyopathy as a chronic disease: A perspective on comprehensive care programs, *Progress in Pediatric*," *Pediatric Cardiology*, vol. 25, pp. 103-111 (2008).

Budts et al., "Residual pulmonary vasoreactivity to inhaled nitric oxide in patients with severe obstructive pulmonary hypertension and Eisenmenger syndrome," *Heart*, vol. 86, pp. 553-558 (2001).

Canadian Office Action mailed May 31, 2011 for Canadian Patent Application No. 2671029, a counterpart foreign application of U.S. Appl. No. 12/494,598.

Clark et al., "Low-Dose Nitric Oxide Therapy for Persistent Pulmonary Hypertension: 1-Year Follow-up," *Journal of Perinatology*, vol. 23, pp. 300-303 (2003).

Clark et al., "Low-Dose Nitric Oxide Therapy for Persistent Pulmonary Hypertension of the Newborn," *New England Journal of Medicine*, vol. 342, No. 7, pp. 469-474 (2000).

Cockrill et al., "Comparison of the Effects of Nitric Oxide, Nitroprusside, and Nifedipine on Hemodynamics and Right Ventricular Contractility in Patients With Chronic Pulmonary Hypertension," *Chest*, vol. 119, No. 1, pp. 128-136 (2001).

Comparison of Supplemental Oxygen and Nitric Oxide for Inhalation in the Evaluation of the Reactivity of the Pulmonary Vasculature During Acute Pulmonary Vasodilator Testing, http://clinicaltrials.gov/archive/NCT00626028/2009_01_12 Jan. 12, 2009.

Cornfield et al., "Randomized, Controlled Trial of Low-dose Inhaled Nitric Oxide in the Treatment of Term and Near-term Infants With Respiratory Failure and Pulmonary Hypertension," *Pediatrics*, vol. 104, No. 5, pp. 1089-1094 (1999).

Cox et al., "Factors Associated with Establishing a Causal Diagnosis for Children with Cardiomyopathy," *Pediatrics*, vol. 118, No. 4, pp. 1519-1531 (2006).

Cujec et al., "Inhaled Nitric Oxide Reduction in Systolic Pulmonary Artery Pressure is Less in Patients with Decreased Left Ventricular Ejection Fraction," *Canadian Journal of Cardiology*, vol. 13(9), pp. 816-824 (1997).

Cuthbertson et al., "UK guidelines for the use of inhaled nitric oxide therapy in adults ICUs," *Intensive Care Med.*, vol. 23, Springer-Verlag, pp. 1212-1218 (1997).

Davidson et al., "Inhaled nitric oxide for the early treatment of persistent pulmonary hypertension of the term newborn: a random-

Davidson et al., "Safety of Withdrawing Inhaled Nitric Oxide Therapy in Persistent Pulmonary Hypertension of the Newborn," *Pediatrics*, vol. 104, No. 2, pp. 231-236 (1999).

Day et al., "Pulmonary Vasodilatory Effects of 12 and 60 Parts Per Million Inhaled Nitric Oxide in Children with Ventricular Septal Defect," *The American Journal of Cardiology*, vol. 75, pp. 196-198 (1995).

Definition of Contraindication on [Medicine.net.com](http://www.medicines.net.com); <http://www.medterms.com/script/main/art.asp?articlekey=17824>; retrieved Mar. 14, 2011; 2 pages.

Delivery of Inhaled Nitric Oxide Therapy through an Adult or Pediatric Nasal Cannula, Reference: UTMB Respiratory Care Services Reviewed: May 31, 2005.

Dickstein et al., "A Theoretic Analysis of the Effect of Pulmonary Vasodilation on Pulmonary Venous Pressure: Implications for Inhaled Nitric Oxide Therapy," *The Journal of Heart and Lung Transplant*, pp. 715-721 (1996).

Dorland, "The American Illustrated Medical Dictionary," 7th edition, W.B. Saunders Company, p. 113 (1914).

Dorling, "Neurodevelopmental outcome following Nitric Oxide Therapy for Persistent Pulmonary Hypertension in Term Newborn Infants," *Neonatal Intensive Care Unit, Leicester Royal Infirmary*, Aug. 8, 2003, modified Nov. 12, 2003, 3 pages.

Douwes et al., "The Maze of Vasodilator Response Criteria," Published online: Nov. 26, 2010, *Pediatr. Cardiol.*, vol. 32, pp. 245-246 (2011).

Ehrenkranz, "Inhaled Nitric Oxide in Full-Term and Nearly Full-Term Infants with Hypoxic Respiratory Failure," *The Neonatal Inhaled Nitric Oxide Study Group*, *N. Engl. J. Med.*, vol. 336, No. 9, pp. 597-605 (1997).

http://www.cc.nih.gov/ccmd/clinical_services.html, page last updated May 19, 2011.

<http://www.medterms.com/script/main/art.asp?articlekey=17824>, Definition of Contraindication, last Editorial Review Mar. 19, 2012.

Ovodov et al., "Nitric Oxide: Clinical Applications," *Seminars in Anesthesia*, Saunders, CO, New York NY, vol. 19, No. 2, pp. 88-97 (2000).

Pazopanib Plus Lapatinib Compared to Lapatinib Alone in Subjects With Inflammatory Breast Cancer, p. 4, *ClinicalTrials.gov*, <<<http://clinicaltrials.gov/ct2/show/NCT00558103>>> Apr. 22, 2010.

PCT/US2010/038652 Search Report dated Jul. 29, 2010, 16 pages.

Pepke-Zaba et al., "Inhaled nitric oxide as a cause of selective pulmonary vasodilation in pulmonary hypertension," *The Lancet*, vol. 338, pp. 1173-1174 (1991).

Ratnasamy et al., "Associations between neurohormonal and inflammatory activation and heart failure in children," *American Heart Journal*, pp. 527-533 (2008).

Response filed Aug. 18, 2010 to EP Search Report dated May 10, 2010 for EP09251949.

Ricciardi et al., "Inhaled Nitric Oxide in Primary Pulmonary Hypertension: A Safe and Effective Agent for Predicting Response to Nifedipine," *Journal of the American College of Cardiology (JACC.)* vol. 32, No. 4, pp. 1068-1073 (1998).

Roberts, "Inhaled Nitric Oxide and Persistent Pulmonary Hypertension of the Newborn," *The New England Journal of Medicine*, vol. 336, No. 9, pp. 605-610 (1997).

Roberts, "Nitric Oxide and the Lung," Marcel Dekker, Inc., New York, NY, pp. 333-363 (1997).

Rosales et al., "Hemodynamic Effects Observed with Inhaled Nitric Oxide After Surgical Repair of Total Anomalous Pulmonary Venous Return," *Pediatric Cardiology*, vol. 20, pp. 224-226 (1999).

Rosenberg, "Inhaled nitric oxide in the premature infant with severe hypoxemic respiratory failure: A time for caution," *The Journal of Pediatrics*, vol. 133, Issue 6, pp. 720-722 (1998).

Sadiq et al., "Inhaled Nitric Oxide in the Treatment of Moderate Persistent Pulmonary Hypertension of the Newborn: A Randomized Controlled, Multicenter Trial," *Journal of Perinatology*, vol. 23, pp. 98-103 (2003).

Search Report from EP 09251949 dated May 10, 2010.

Sehgal et al., "Experience with Inhaled Nitric Oxide Therapy in

(56)

References Cited

OTHER PUBLICATIONS

- Semigran et al., "Hemodynamic Effects of Inhaled Nitric Oxide in Heart Failure," *Journal of American College of Cardiology (JACC)*, vol. 24, No. 4, pp. 982-988 (1994).
- Shapiro et al., "Diagnostic Dilemmas: Diastolic Heart Failure Causing Pulmonary Hypertension and Pulmonary Hypertension Causing Diastolic Dysfunction," *Advances in Pulmonary Hypertension*, vol. 5(1), pp. 13-20 (2006) http://www.phaonlineuniv.org/sites/default/files/spr_2006.pdf.
- Sibutramine-metformin Combination vs. Sibutramine and Metformin Monotherapy in Obese Patients, p. 3, *ClinicalTrials.gov*, <<<http://clinicaltrials.gov/ct2/show/NCT00941382>>> Sponsored by Laboratorios Silanes S.A. de C.V. and Jorge González Canudas, Jul. 15, 2009.
- Singh et al., "Nitric Oxide, the biological mediator of the decade: fact of fiction?," *Eur. Respir. J.*, vol. 10, pp. 699-707 (1997).
- Smyth, "Inhaled nitric oxide treatment for preterm infants with hypoxic respiratory failure," *Thorax*, vol. 55 (Suppl 1), pp. S51-S55 (2000).
- Somarrriba et al., "Exercise rehabilitation in pediatric cardiomyopathy," *Progress in Pediatric Cardiology*, vol. 25, pp. 91-102 (2008).
- Soto et al., "Cardiopulmonary Hemodynamics in Pulmonary Hypertension: Pressure Tracings, Waveforms, and More," *Advances in Pulmonary Hypertension Winter*, vol. 7(4), pp. 386-393 (2008).
- Steinhorn et al., "Inhaled nitric oxide enhances oxygenation but not survival in infants with alveolar capillary dysplasia," *The Journal of Pediatrics*, pp. 417-422 (1997).
- Steinhorn, "Persistent Pulmonary Hypertension in the Newborn and Infant," vol. 1(2), pp. 287-299 (1987) [downloaded from www.Emedicine.com on Jun. 10, 2008].
- Steinhorn, "Pulmonary Hypertension, Persistent-Newborn," Updated Apr. 19, 2007, <http://emedicine.medscape.com/article/898437-overview>.
- Stuedel et al., "Inhaled nitric oxide," *Anesthesiology*, vol. 91, pp. 1090-1121 (1999).
- Strauss et al., "Pediatric Cardiomyopathy—A Long Way to Go," *The New England Journal of Medicine*, vol. 348, No. 17, pp. 1703-1705 (2003).
- Toshniwal, et al., "Study of Comparative Effects of Oral Clonidine vs. Oral Diazepam Pre-Medication on the Extent and Duration of Sensory Blockade in Patients Undergoing Vaginal Hysterectomy Under Spinal Anaesthesia", *InterenetJournal of Anesthesiology* (2009) <<<http://www.britannica.com/bps/additionalcontent/18/41575551/Study-of-Comparative-Effects-Oral-Clonidine-vs-Oral-Diazepam-Pre-Medication-on-the-Extent-and-Duration-of-Sensory-Blockade-in-Patients-Undergoing-Vaginal-Hysterectomy-Under-Spinal-Anaesthesia>>>.
- The American Illustrated Medical Dictionary (Dorland, 7th ed., p. 113) (1914).
- The Effects of Nitric Oxide for Inhalation on the Development of Chronic Lung Disease in Pre-Term Infants, from *ClinicalTrials.gov* archive, NCT00551642, Oct. 30, 2007, 3 pages.
- The Encarta Webster's Dictionary of the English Language (2004) is the second edition of the Encarta World Dictionary, published 1999, <<<http://encarta.msn.com/encnet/features/dictionary/dictionaryhome.aspx>>>; used to look up the definitions of "precaution" and "exclusion".
- The Neonatal Inhaled Nitric Oxide Study Group, *The New England Journal of Medicine*, vol. 336(9), pp. 597-604 (1997).
- The NIH, Critical Care Therapy and Respiratory Care Section, *Nitric Oxide Therapy*, 13 pages (2000).
- Towbin et al., "Incidence, Causes, and Outcomes of Dilated Cardiomyopathy in Children," *JAMA*, vol. 296, No. 15, pp. 1867-1876 (2006).
- Translated Japanese Office Action mailed Feb. 15, 2011 for Japanese Patent Application No. 2009-157623, a counterpart foreign application for U.S. Appl. No. 12/494,598.
- UCI General Clinical Research Center, Federal Regulations 21 CFR Part 312, <<<http://www.gcrc.uci.edu/rsa/aer.cfm>>>, retrieved Sep. 13, 2010, 2 pages.
- University of Alabama, NCT00732537 at *Clinicaltrials.gov* (2008). "Use of Inhaled Nitric Oxide," *American Academy of Pediatrics—Committee on Fetus and Newborn, Pediatrics* vol. 106, No. 2, pp. 344-345 (2000).
- UTMB Respiratory Care Services, "Delivery of Inhaled Nitric Oxide Therapy through an Adult or Pediatric Nasal Cannula," 4 pages, (2003).
- van Dalen, "Treatment for Asymptomatic Anthracycline-Induced Cardiac Dysfunction in Childhood Cancer Survivors: The Need for Evidence," *Journal of Clinical Oncology*, vol. 21, No. 17, pp. 3375-3379 (2003).
- Watson et al., "Clinical and Economic Effects of iNO in Premature Newborns With Respiratory Failure at 1 Year", *Pediatrics*, vol. 124, pp. 1333-1343 (2009).
- Weinberger et al., "The Toxicology of Inhaled Nitric Oxide," *Toxicological Sciences*, vol. 59, pp. 5-16 (2001).
- Weinberger et al., "Nitric Oxide in the lung: therapeutic and cellular mechanisms of action", *Pharmacology & Therapeutics*, vol. 84, pp. 401-411 (1999).
- Wessel et al., "Improved Oxygenation in a Randomized Trial of Inhaled Nitric Oxide for Persistent Pulmonary Hypertension of the Newborn," *Pediatrics*, vol. 100, No. 5, p. E7 (1997).
- Wessel et al., "Managing low cardiac output syndrome after congenital heart surgery," *Crit. Care Med.*, vol. 29(10) pp. S220-S230 (2001).
- Wheeler et al., "The Central Nervous System in Pediatric Critical Illness and Injury," *Pediatric Critical Care Medicine*, Springer, p. 278 (2007).
- Wilkinson et al., "Epidemiological and outcomes research in children with pediatric cardiomyopathy; discussions from the international workshop on primary and idiopathic cardiomyopathies in children," *Progress in Pediatric Cardiology*, vol. 25, pp. 23-25 (2008).
- Yoshida, "Well-illustrated Diagnostics and Treatment of Heart Failure," Professor of Kawasaki Medical University, cardiovascular internal medicine, *Circulation, Up-to-Date* vol. 2, No. 4, pp. 23-28 (2007).
- Fish & Richardson P.C., Supplemental Remarks in U.S. Appl. No. 12/821,020, filed May 9, 2012 (22 pages).
- Fish & Richardson P.C., Statement of the Substance of the Interview and Comments on Examiner's Interview Summary, in U.S. Appl. No. 12/821,020, mailed Jan. 25, 2012, filed Feb. 27, 2012 (7 pages).
- Examiner's Answer in U.S. Appl. No. 12/820,866, mailed Nov. 2, 2011 (27 pages).
- Fish & Richardson P.C., Express Abandonment in U.S. Appl. No. 12/820,866, filed Dec. 3, 2012 (1 page).
- Eibl et al., "Long-term serial echocardiographic examination of late anthracycline cardiotoxicity and its prevention by dexrazoxane in paediatric patients," *Eur. J. Pediatr.*, vol. 164, pp. 678-684 (2005).
- EP 09251949 Office Action dated Oct. 11, 2010, 5 pages.
- Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), NCT00005773 at *ClinicalTrials.gov* (2008).
- European Patent Office minutes of oral proceedings in EP 09 251 949.5, with allowable claims (7 pages), dated May 23, 2012.
- Fauci et al., *Harrison's Principles of Internal Medicine*, pp. 1287-1291 and 1360, 12th edition, McGraw Hill (1998).
- Federal Regulations 21 CFR Part 312, <<<http://www.gcrc.uci.edu/rsa/aer.cfm>>>, Dec. 3, 2012.
- Ferguson et al., "Inhaled nitric oxide for hypoxemic respiratory failure: Passing bad gas?," *Canadian Medical Association Journal*, vol. 162 (1), pp. 85-86 (2000).
- Field, "Neonatal Ventilation With Inhaled Nitric Oxide Versus Ventilatory Support Without Inhaled Nitric Oxide for Preterm Infants With Severe Respiratory Failure: The INNOVO Multicentre Randomised Controlled Trial (ISRCTN 17821339)," *Pediatrics Journal*, vol. 115, pp. 926-936 (2005) DOI: 10.1542/peds.2004-1209.
- Figure from Dr. Green's presentation given Jan. 10, 2011; 1 page.
- Findlay, "Paradoxical Haemodynamic Response to Inhaled Nitric

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