IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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

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

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

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

1. I am the inventor of the subject matter claimed in the present application.

2. I have over 25 years of experience as a physician, and over 15 years of experience directing clinical research in the pharmaceutical industry.

3. I held the position of Vice President of Clinical Research at Ikaria, Inc. (Ikaria), the assignee of U.S. Patent Application No. 12/821,020, from October 2003 until September 2013. I currently serve as a paid consultant of Ikaria and its subsidiary INO Therapeutics LLC, and retain an equity interest in the company. My *curriculum vitae* is attached as Exhibit 1.

4. Ikaria markets pharmaceutical grade nitric oxide (NO) gas under the brand name INOMAX® (nitric oxide) for inhalation. INOMAX® was approved by the U.S. Food and Drug Administration (FDA) in December 1999, after extensive clinical study and FDA review, for the treatment of term and near-term (>34 weeks) neonates with hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension, where it improves oxygenation and reduces the need for extracorporeal membrane oxygenation (ECMO).

5. Upon approval of INOMAX®, and up to the time the present invention was made, the INOMAX® label contained language communicating, in pertinent part, the following general warnings and contraindication:

> *INOmax® should not be discontinued abruptly, as it may result in an increase in pulmonary artery pressure (PAP) and/or worsening of blood oxygenation (PaO_2).*
>
> *Deterioration in oxygenation and elevation in PAP may also occur in children with no apparent response to INOmax....*
>
> *Methemoglobinemia increases with the dose of nitric oxide. ... Following discontinuation or reduction of nitric oxide the methemoglobin levels returned to baseline over a period of hours....*
>
> *INOmax should be administered with monitoring for PaO_2, methemoglobin and NO_2....*
>
> *INOmax® should not be used in the treatment of neonates known to be dependent on right-to-left shunting of blood.*

Thus, the original INOMAX® label did not include any warning or precaution with respect to a risk of pulmonary edema in patients with pre-existing left ventricular dysfunction (LVD).

6. In May 2004, INO Therapeutics LLC[1] (INOT) initiated a clinical trial entitled "Comparison of Supplemental Oxygen and Nitric Oxide for Inhalation Plus Oxygen in the Evaluation of the Reactivity of the Pulmonary Vasculature During Acute Pulmonary Vasodilator Testing," designated the "INOT22" trial, to compare the utility and side effects of oxygen (O_2), inhaled NO, and a combination of inhaled NO and O_2 for determining pulmonary reactivity. I was the Medical Monitor responsible for the design and execution of the INOT22 study.

7. The INOT22 study was a randomized, multi-center study having an expected enrollment of 150 patients in approximately 18 study sites over approximately 2 years. The expected patient population for enrollment into the INOT22 study was subjects between the ages of four weeks and 18 years with idiopathic pulmonary arterial hypertension, congenital heart disease (with or without intravascular shunt) with pulmonary hypertension, or a cardiomyopathy, and who were undergoing diagnostic right heart catheterization scheduled to include acute pulmonary vasodilation testing to assess pulmonary vasoreactivity. The purpose of the study was to assess the safety and effectiveness of inhaled NO as a diagnostic agent in pediatric patients undergoing assessment of pulmonary hypertension (primary objective), and to confirm the hypothesis that inhaled NO is selective for the pulmonary vasculature (secondary objective).

[1] INO Therapeutics LLC is a wholly owned subsidiary of Ikaria, Inc., and holder of the NDA for INOMAX®.

8. The INOT22 study was established and designed by the study sponsor (INOT) and a Steering Committee comprising internationally recognized experts in the field of pediatric heart and lung disease, whose members assisted INOT in developing the INOT22 protocol, monitor the progress of the trial, and provide recommendations to INOT on changes in the procedures and conduct of the trial.

9. The Steering Committee consisted of:

a. David L. Wessel, MD, presently Senior Vice President, The Center for Hospital Based Specialties, and Division Chief, Pediatric Critical Care Medicine, at Children's National Medical Center, Washington, DC;

b. Robyn J. Barst, MD, formerly Professor Emeritus of Pediatrics and Medicine, Columbia University College of Physicians and Surgeons, New York; and

c. Duncan J. Macrae, MD, presently Director, Pediatric Intensive Care, Royal Brompton Hospital, London, UK.

10. The original INOT22 study protocol designed by INOT and the Steering Committee did not exclude study patients with pre-existing left ventricular dysfunction who were not dependent on right-to-left shunting of blood. The original INOT22 protocol designed by INOT and the Steering Committee contained the following inclusion and exclusion criteria:

Inclusion Criteria

The patient must meet the following criteria:

1. Have any one of the three disease categories:

a. Idiopathic Pulmonary Arterial Hypertension

i. PAPm >25mmHg at rest, PCWP≤ 15mmHg, and PVRI>3 u·m^2 or diagnosed clinically with no previous catheterization.

b. CHD with pulmonary hypertension repaired and unrepaired,

i. PAPm > 25mmHg at rest, and PVRI >3 u· m^2 or diagnosed clinically with no previous catheterization.

c. Cardiomyopathy

i. PAPm>25mmHg at rest, and PVRI>3u·m^2 or diagnosed clinically with no previous catheterization.

2. Scheduled to undergo right heart catheterization to assess pulmonary vasoreactivity by acute pulmonary vasodilation testing.

3. Males or females, ages 4 weeks to 18 years, inclusive.

4. Signed IRB/IEC approved informed consent (and assent if applicable).

Exclusion Criteria

The patent will be excluded from enrollment if any of the following are true:

1. Focal pulmonary infiltrates on chest radiograph.

2. Diagnosed with severe obstructive or restrictive pulmonary disease that is significantly contributing to the patient's pulmonary hypertension.

3. Received treatment with nitric oxide for inhalation within 30 days prior to study initiation, are on other investigational medications, nitroglycerin, sodium nitroprusside, sildenafil, other PDE-5 inhibitors, or prostacyclin.

4. Pregnant (urine HCG +).

11. After the INOT22 study protocol design, but prior to study initiation and enrollment, the original INOT22 study protocol was reviewed by an Institutional Review Board (IRB) and/or Independent Ethics Committee (IEC) at each of the 18 participating study institutions, including review by the principal investigator within each study institution. In addition, prior to study initiation and enrollment, the original INOT22 study protocol was reviewed by the US Food and Drug Administration (FDA) and separately reviewed by each national Health Authority (European equivalent to FDA) within the four European countries participating in the INOT22 trial (United Kingdom, France, Netherlands and Spain). Further, INOT regularly requested input and scientific guidance on the clinical trial from its own

Scientific Advisory Board. At no time did any member of the Steering Committee, INOT, an IRB or IEC, an individual principal investigator, a Scientific Advisory Board member, FDA or European Health Authority suggest that subjects with pre-existing left ventricular dysfunction who are not dependent on right-to-left shunt should be excluded from the INOT22 study or that such subjects would be predicted to have an increased risk of adverse events or serious adverse events arising from the administration to them of inhaled nitric oxide.

12. Under FDA regulations, an IRB is an appropriately constituted group that has been formally designated to review and monitor biomedical research involving human subjects. In accordance with FDA regulations, an IRB has the authority to approve, require modifications in (to secure approval), or disapprove research. This group review serves an important role in the protection of the rights and welfare of human research subjects. The purpose of IRB review is to assure, both in advance and by periodic review, that appropriate steps are taken to protect the rights and welfare of humans participating as subjects in the research. To accomplish this purpose, IRBs use a group process to review research protocols to ensure protection of the rights and welfare of human subjects of research. An IRB must have at least five members and each member must have enough experience, expertise and diversity to make an informed decision on whether the research is ethical, informed consent is sufficient and the appropriate safeguards have been put in place (see 21 CFR Part 56).

13. In Europe, an IEC is an independent body in an EC Member State consisting of healthcare professionals and non-medical members whose responsibility is to protect the rights, safety and well-being of human subjects involved in a clinical trial and to provide public assurance of that protection by expressing an opinion on a proposed clinical trial protocol, the suitability of the investigators, and the adequacy of facilities involved in a trial (see Directive 2001/20/EC).

14. In total, at least 115 individuals experienced in and responsible for the review of clinical trial protocols for patient safety, in addition to the FDA and four European Health Authorities, reviewed the original INOT22 protocol prior to initiation of the INOT22 study.

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