Mallinckrodt Announces Positive Findings in INOmax® (Nitric Oxide) Gas, for Inhalation Phase 4 Observational Registry in Neonates with Pulmonary Hypertension; Ends Trial Early

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- Company ends Phase 4 observational registry early as data achieved statistical significance for non-inferiority in premature neonates compared to term and near-term neonates at planned interim analysis -

STAINES-UPON-THAMES, United Kingdom, May 4, 2020 /PRNewswire/ -- Mallinckrodt plc (NYSE: MNK), a global biopharmaceutical company, today announced that its observational registry comparing the safety and effectiveness of INOmax® (nitric oxide) gas, for inhalation, in term and near-term neonates to that in preterm neonates with pulmonary hypertension (PH) was ended early due to achievement of the pre-specified primary outcome measure, non-inferiority (95 percent confidence interval: -0.0021, 0.1158, with a pre-defined margin of -0.1452). The decision was made following the second planned interim analysis at 75 percent enrollment. The company intends to share the results of this study in an appropriate scientific forum soon.

INOmax is indicated for the treatment of term and near-term neonates with hypoxic respiratory failure associated with pulmonary hypertension. The safety and efficacy of INOmax in premature neonates has not been evaluated by the U.S. Food and Drug Administration.

Persistent pulmonary hypertension of the newborn (PPHN) is a serious and sometimes fatal cardiorespiratory complication of the transition to extra-uterine life.[1,2] The registry trial was conducted to examine the utility of INOmax in pre-term neonates. Due to the seriousness of the condition, a randomized controlled trial cannot be conducted in the pre-term neonate population.

"Mallinckrodt is extremely pleased to be able to end this registry based on positive findings much earlier than anticipated," **said Steven Romano, M.D., Executive Vice President and Chief Scientific Officer at Mallinckrodt**. "The real-world data provided by this registry underscores our commitment to continue to expand upon the body of scientific knowledge on treatment of vulnerable patient populations, such as premature infants with pulmonary hypertension."

The observational registry study was conducted across 31 sites and was designed to evaluate the effectiveness and safety of INOmax in 168 premature neonates vs term and near-term neonates (1:1) with PH. The interim analysis assessed 54 premature and 84 term and near-term neonates and demonstrated that the trial achieved the significance level for non-inferiority. Evaluation of significant improvement for each neonate is based on at least a 25 percent decrease in oxygenation index (OI) or surrogate OI (SOI) during the INOmax treatment period.

No drug-related serious adverse events were attributed to study drug. At the time of the interim analysis, there were 17 adverse events of special interest reported in 16 subjects, most of which were in the preterm group and deemed not related or unlikely related to study drug.

INOmax has been on the market in the U.S. since 2000 and 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. Please see Important Safety Information below.

About the Observational Registry

- The **Registry Evaluating Premature and Term and Near-Term Neonates with Pulmonary Hypertension Receiving Inhaled Nitric Oxide (PaTTerN)** is a multicenter, prospectively defined, observational registry study to evaluate the use of INOmax to treat pulmonary PH in premature neonates (27 to less than 34 weeks gestational age) and term and near-term neonates (34 to 40 weeks gestational age).
- The primary outcome measure compares the incidence of subjects with at least a 25 percent improvement (decrease) from baseline in OI or SOI during the INOmax treatment period in pre-term vs term and near-term neonates with PH.
- Secondary efficacy endpoints include:
    - The incidence of subjects with at least a 25 percent improvement in OI/SOI in each severity group of mild, moderate and severe
    - The time to response to INOmax up to 96 hours for each severity and age group
    - Evaluation of 25 percent improvement in OI/SOI with univariate and multivariate logistic regressions for baseline factors: age and severity group, disease subtype, weight, race, gender
    - The incidence of partial responders (< 25 percent improvement in OI/SOI) and non-responders (< 5 percent improvement in OI/SOI) summarized by age group and by each severity group within each age group
- Patients were classified as mild, moderate or severe based on a primary measure of OI or a secondary measure of SOI for hypoxic respiratory failure (HRF) severity:

    - Mild: OI < 16 or SOI < 10
    - Moderate: OI value 16 to 25 or SOI value 10 to 15
    - Severe: OI >25 or SOI >15
- Patients were evaluated for response to INOmax and safety during a treatment period of up to 96 hours ± 12 hours and a safety follow-up through 7 days (for a total of up to 11 days) or to hospital discharge, whichever came first

More information about the trial can be found here.

Study Limitations
The current study is a prospective observational registry that collects real world data that describes how INOmax nitric oxide gas is being used in clinical practice. As an observational study it does not utilize placebo. Hence, some of the improvement observed in the current study could be due to factors other than treatment with INOmax. Similarly, without placebo control it is not possible to understand the magnitude to which patients who experienced limited response to inhaled nitric oxide would have otherwise decompensated without this treatment.

About Persistent Pulmonary Hypertension of the Newborn (PPHN)
PPHN is a serious and sometimes fatal cardiorespiratory complication of the transition to extra-uterine life.[1,2] PPHN is a clinical syndrome associated with various neonatal cardiorespiratory diseases, including meconium aspiration, respiratory distress syndrome (hyaline membrane disease), congenital heart disease and congenital hernia.[1] Despite the diversity of causes, marked pulmonary vasoconstriction is the central pathophysiologic feature of PPHN.[3] The most significant hemodynamic feature in neonates with severe hypoxia is a pulmonary-to-systemic pressure imbalance.[4] Treatment in these neonates is directed toward lowering the pulmonary vascular pressure and supporting the systemic circulation.[1,3]

INDICATION

INOmax® (nitric oxide) gas, for inhalation, 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.

IMPORTANT SAFETY INFORMATION

- INOmax is contraindicated in the treatment of neonates dependent on right-to-left shunting of blood.
- Abrupt discontinuation of INOmax may lead to increasing pulmonary artery pressure and worsening oxygenation.
- Methemoglobinemia and NO_2 levels are dose dependent. Nitric oxide donor compounds may have an additive effect with INOmax on the risk of developing methemoglobinemia. Nitrogen dioxide may cause airway inflammation and damage to lung tissues.
- In patients with pre-existing left ventricular dysfunction, INOmax may increase pulmonary capillary wedge pressure leading to pulmonary edema.
- Monitor for PaO_2, inspired NO_2, and methemoglobin during INOmax administration.
- INOmax must be administered using a calibrated FDA-cleared Nitric Oxide Delivery System.

Please see Full Prescribing Information.

ABOUT MALLINCKRODT
Mallinckrodt is a global business consisting of multiple wholly owned subsidiaries that develop, manufacture, market and distribute specialty pharmaceutical products and therapies. The company's Specialty Brands reportable segment's areas of focus include autoimmune and rare diseases in specialty areas like neurology, rheumatology, nephrology, pulmonology and ophthalmology; immunotherapy and neonatal respiratory critical care therapies; analgesics and gastrointestinal products. Its Specialty Generics reportable segment includes specialty generic drugs and active pharmaceutical ingredients. To learn more about Mallinckrodt, visit www.mallinckrodt.com.

Mallinckrodt uses its website as a channel of distribution of important company information, such as press releases, investor presentations and other financial information. It also uses its website to expedite public access to time-critical information regarding the company in advance of or in lieu of distributing a press release or a filing with the U.S. Securities and Exchange Commission (SEC) disclosing the same information. Therefore, investors should look to the Investor Relations page of the website for important and time-critical information. Visitors to the website can also register to receive automatic e-mail and other notifications alerting them when new information is made available on the Investor Relations page of the website.

CAUTIONARY STATEMENTS RELATED TO FORWARD-LOOKING STATEMENTS
This release includes forward-looking statements concerning inhaled nitric oxide ("iNO") and the Company's iNO product, including statements with regard to the clinical data generated in the study described above. The statements are based on assumptions about many important factors, including the following, which could cause actual results to differ materially from those in the forward-looking statements: satisfaction of regulatory and other requirements; actions of regulatory bodies and other governmental authorities; changes in laws and regulations; issues with product quality, manufacturing or supply, or patient safety issues; and other risks identified and described in more detail in the "Risk Factors" section of Mallinckrodt's most recent Annual Report on Form 10-K and other filings with the SEC, all of which are available on its website. The forward-looking statements made herein speak only as of the date hereof and Mallinckrodt does not assume any obligation to update or revise any forward-looking statement, whether as a result of new information, future events and developments or otherwise, except as required by law.

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