DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 106088
NDA 020845

WRITTEN REQUEST

INO Therapeutics
6 Route 173
Clinton, New Jersey 08809

Attention: Mary Ellen Anderson
Senior Director, Regulatory Affairs

Dear Ms. Anderson:

Reference is made to your April 14, 2008, Proposed Pediatric Study Request for INOmax (nitric oxide) for inhalation.

BACKGROUND:

These studies investigate the potential use of nitric oxide in the treatment of bronchopulmonary dysplasia in premature infants.

Bronchopulmonary dysplasia (BPD) in premature infants is associated with prolonged hospitalization and the co-morbidities of abnormal pulmonary and neurodevelopmental outcomes. Inhaled nitric oxide is approved to treat term infants for respiratory failure associated with pulmonary hypertension and has been reported to decrease pulmonary artery pressure and improve gas exchange. There are experimental data that suggest inhaled nitric oxide could benefit premature infants by reducing the risk for development of BPD; however, the precise mechanism(s) by which inhaled nitric oxide might improve lung function and decrease the risk of BPD remains uncertain. While the findings of several large, controlled studies to assess the efficacy of inhaled nitric oxide in reducing the incidence of BPD have been mixed, inhaled nitric oxide is used off-label as a therapy for premature infants with respiratory failure. Alternative therapies to reduce the risk of BPD include administration of corticosteroids to the mother prenatally and the use of a pulmonary surfactant.

To obtain needed pediatric information on the use of nitric oxide in the premature infant population, the Food and Drug Administration (FDA) is hereby making a formal Written Request (WR), pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act (the Act), as amended by the Food and Drug Administration Amendments Act of 2007, that you submit information from the studies described below.

- *Nonclinical studies:*

  Based on review of the available nonclinical toxicology, no additional animal studies are required at this time to support the clinical studies described in this written request.

- *Clinical studies*:

  Study 1: Double-blind, placebo-controlled, randomized efficacy and safety trial

  Study 2: Double-blind, placebo-controlled, randomized efficacy and safety trial

  Efficacy in preterm neonates cannot be extrapolated and will be assessed by the studies outlined in this WR.

- *Objective of this study:*

  Study 1: To assess the effect of nitric oxide on survival without bronchopulmonary dysplasia (BPD) in preterm neonates with respiratory distress who require ventilatory assistance.

  Study 2: To assess the effect of nitric oxide on reducing the risk of chronic lung disease (CLD) preterm neonates at high risk of developing CLD.

- *Patients to be studied:*

  Study 1: Approximately 800 neonates > 500 grams, < 24 hours old, and 24-28 weeks gestational age.

  Study 2: Approximately 587 preterm infants < 32 weeks gestational age and 500 to 1250 grams at birth, 7-21 days old.

  Representation of ethnic and racial minorities: The studies must take into account adequate (e.g., proportionate to disease population) representation of children of ethnic and racial minorities. If you are not able to enroll an adequate number of these patients, provide a description of your efforts to do so and an explanation for why they were unsuccessful.

- *Study endpoints:*

  Study 1
  - *Efficacy endpoints:*
    Primary: Survival without BPD as defined by the need for supplemental oxygen at 36 weeks postmenstrual age in preterm neonates with respiratory distress. An infant who is alive without chronic lung disease (CLD) at 36 weeks postmenstrual age will be counted as a "success." Any infant who has died, or who has developed CLD at 36 weeks postmenstrual age will be counted as a "failure."

  Study 2
  - *Efficacy endpoints*:
    - Improvement in survival without CLD at 36 weeks postmenstrual age in preterm neonates.

- Reduction in the need for supplemental oxygen at 36 weeks postmenstrual age.

- *Known drug safety concerns and monitoring:*
  - Methemoglobinemia
  - Elevated nitrogen dioxide concentrations
  - Retinopathy of prematurity
  - Intraventricular hemorrhage

  While not a requirement for this Written Request, long-term neurodevelopmental outcome data at 2 and 7 years corrected age and pulmonary function testing at 7 years corrected age should be submitted when available.

- *Extraordinary results:* In the course of conducting these studies, you may discover evidence to indicate that there are unexpected safety concerns, unexpected findings of benefit in a smaller sample size, or other unexpected results. In the event of such findings, there may be a need to deviate from the requirements of this Written Request. If you believe this is the case, you must contact the Agency to seek an amendment. It is solely within the Agency's discretion to decide whether it is appropriate to issue an amendment.

- *Drug information:* nitric oxide for inhalation or placebo

  - *Dosage form*: gas for inhalation

  - *Route of administration*: administered using a blinded version of the INOvent® delivery system by introducing the study gas into the inspiratory limb of the ventilator circuit.

  - *Regimen*:

    Study 1: Nitric oxide will be administered at 5 ppm. Therapy will be initiated ideally within 2 hours but no later than 26 hours after birth. Treatment will continue for a minimum of 7 days, or until the end of ventilatory support (whichever is later), and up to 21 days maximum. Patient who require less than 7 days of assisted ventilation may complete the minimum duration of therapy via face mask or nasal cannula.

    Study 2: Beginning at 7 to 21 days of age, nitric oxide will be administered at 20 ppm or less for 48 to 96 hours. After this time, it will be weaned to 10 ppm. After one week at 10 ppm, it will be weaned to 5 ppm. After one week at 5 ppm, it will be lowered to 2 ppm. After one week at 2 ppm, the nitric oxide will be discontinued. The total duration of therapy will be 23-25 days.

- *Statistical information, including power of study and statistical assessments:*

  Study 1: The study will be powered at 80% at a 0.01 alpha level to detect a 20% difference in the rate of survival without BPD at 36 weeks postmenstrual age.

Study 2: A sample size of 585 randomized infants will have 80% power to detect a 12% difference (50-62%) in the rate of survival without chronic lung disease while controlling for a two-sided alpha of 0.05, allowing for two interim analyses at approximately 20% and 50% of the outcome data available.

- *Labeling that may result from the studies*: You must submit proposed pediatric labeling to incorporate the findings of the studies. Under section 505A(j) of the Act, regardless of whether the studies demonstrate that nitric oxide is safe and effective, or whether such study results are inconclusive in the studied pediatric population(s) or subpopulation(s), the labeling must include information about the results of the studies. Under section 505A(k)(2) of the Act, you must distribute to physicians and other health care providers at least annually (or more frequently if FDA determines that it would be beneficial to the public health), information regarding such labeling changes that are approved as a result of the studies.

- *Format and types of reports to be submitted*: You must submit full study reports (which have not been previously submitted to the Agency), including the prospective statistical analysis plans, if available, that address the issues outlined in this request, with full analysis, assessment, and interpretation. In addition, the reports must include information on the representation of pediatric patients of ethnic and racial minorities. All pediatric patients enrolled in the studies should be categorized using one of the following designations for race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander, or White. For ethnicity, you should use one of the following designations: Hispanic/Latino or Not Hispanic/Latino. If you choose to use other categories, you should obtain agency agreement.

  Under section 505A(d)(2)(B) of the Act, when you submit the study reports, you must submit all postmarketing adverse event reports regarding this drug that are available to you at that time. All postmarket reports that would be reportable under section 21 CFR 314.80 should include adverse events occurring in an adult or a pediatric patient. In general, the format of the postmarket adverse event report should follow the model for a periodic safety update report described in the Guidance for Industry *E2C Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs* and the Guidance addendum. You are encouraged to contact the Division of Pulmonary, Allergy, and Rheumatology Products for further guidance.

  Although not currently required, we request that study data be submitted electronically according to the Study Data Tabulation (SDTM) standard published by the Clinical Data Interchange Standards Consortium (CDISC) provided in the document *Study Data Specifications*, available at http://www.fda.gov/CDER/REGULATORY/ersr/Studydata.pdf and referenced in the Guidance for Industry *Providing Regulatory Submissions in Electronic Format - Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications* available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf.

- *Timeframe for submitting reports of the studies:* Reports of the above studies must be submitted to the Agency on or before December 31, 2010. Please keep in mind that pediatric exclusivity attaches only to existing patent protection or exclusivity that would otherwise expire nine (9) months or more after pediatric exclusivity is granted, and FDA has 180 days from the date that the study reports are submitted to make a pediatric exclusivity determination. Therefore, to ensure that a particular patent or exclusivity is eligible for pediatric exclusivity to attach, you are advised to submit the reports of the studies at least 15 months (9 months plus 6 months/180 days for determination) before such patent or exclusivity is otherwise due to expire.

- *Response to Written Request:* Under section 505A(d)(2)(A)(i), within 180 days of receipt of this Written Request, you must notify the Agency whether or not you agree to the Written Request. If you agree to the request, you must indicate when the pediatric studies will be initiated. If you do not agree to the request, you must indicate why you are declining to conduct the studies.

  Furthermore, if you agree to conduct the studies, but have not submitted the study reports on or before the date specified in the Written Request, the Agency may utilize the process discussed in section 505A(n) of the Act.

Submit protocols for the above studies to an investigational new drug application (IND) and clearly mark your submission "**PEDIATRIC PROTOCOL SUBMITTED FOR PEDIATRIC EXCLUSIVITY STUDY**" in large font, bolded type at the beginning of the cover letter of the submission.

Reports of the studies should be submitted as a new drug application (NDA) or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, clearly mark your submission "**SUBMISSION OF PEDIATRIC STUDY REPORTS - PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED**" in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter. Please also send a copy of the cover letter of your submission to the Director, Office of Generic Drugs, HFD-600, Metro Park North IV, 7519 Standish Place, Rockville, MD 20855-2773. If you wish to fax it, the fax number is 240-276-9327.

In accordance with section 505A(k)(1) of the Act, *Dissemination of Pediatric Information*, FDA must make available to the public the medical, statistical, and clinical pharmacology reviews of the pediatric studies conducted in response to this Written Request within 210 days of submission of your study report(s). These reviews will be posted regardless of the following circumstances:

1. the type of response to the Written Request (i.e., complete or partial response);
2. the status of the application (i.e., pending or withdrawn after the supplement has been filed);
3. the action taken (i.e., approval, complete response); or
4. the exclusivity determination (i.e., granted or denied).

FDA will post the medical, statistical, and clinical pharmacology reviews on the FDA website at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM049872.

If you wish to discuss any amendments to this Written Request, submit proposed changes and the reasons for the proposed changes to your application. Submissions of proposed changes to this request should be clearly marked "**PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES**" in large font, bolded type at the beginning of the cover letter of the submission. You will be notified in writing if any changes to this Written Request are agreed upon by the Agency.

Please note that, if your trial is considered an "applicable clinical trial" under section 402(j)(1)(A)(i) of the Public Health Service Act (PHS Act), you are required to comply with the provisions of section 402(j) of the PHS Act with regard to registration of your trial and submission of trial results. Additional information on submission of such information is available at www.ClinicalTrials.gov.

If you have any questions, call Angela Robinson, Regulatory Project Manager, at 301-796-2284.

Sincerely,

{See appended electronic signature page}

Curtis J. Rosebraugh, M.D., M.P.H.
Director
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-20845	GI-1	INO THERAPEUTICS INC	INO MAX (NITRIC OXIDE) FOR INHALATION

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CURTIS J ROSEBRAUGH
04/30/2010