# 1 TITLE PAGE

*MEDICAL UNIVERSITY OF SOUTH CAROLINA*

**Study Protocol**

**A Proof of Concept Study of Inhaled Nitric Oxide for Adults with Pulmonary Non-Tuberculous Mycobacterial Infection**

**IND Number: 140649**

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## 2 PROTOCOL SYNOPSIS

| | |
|---|---|
| **Title** | A Proof of Concept Study of Inhaled Gaseous Nitric Oxide (gNO) for Adults with Pulmonary Non-Tuberculous Mycobacterial (NTM) Infection |
| **Clinical Phase** | Phase 2 |
| **Objective** | To evaluate the efficacy and safety of open-label exposure of gNO in patients with NTM lung disease |
| **Endpoints** | Primary<br>• Culture growth (positive or negative) at end of treatment (EOT) compared to baseline<br>Secondary<br>• Safety and tolerability assessments based on adverse events (AEs), clinical values (i.e., methemoglobin levels)<br>• Semiquantitative mycobacterial culture results comparing EOT to baseline<br>Exploratory<br>• Time to positive mycobacterial cultures comparing EOT to baseline<br>• Measures of systemic inflammation comparing EOT to baseline<br>• Absolute change in quality of life scores from baseline to EOT |
| **Study Population** | Adult subjects with NTM lung disease and persistently positive mycobacterial sputum cultures |
| **Number of Subjects** | 10 |
| **Number of sites** | 2 |
| **Study Duration** | Subjects will be treated for 3 weeks (5 days per week) and followed monthly for 3 months |
| **Study Design** | This 2 study is designed to evaluate the efficacy and safety of open-label gNO treatment in subjects with NTM lung disease and persistently positive sputum cultures growing NTM. This is a proof-of-concept study in which all subjects will be treated with gNO (i.e. no control) to see if there can be a microbiological effect by conversion to negative sputum cultures and how long that effect can be sustained following treatment. In addition, this study will assess the feasibility of such a treatment course in this patient population and measure relevant clinical outcomes (e.g. cough, quality of life). Subjects will provide sputum for culture at baseline, weekly during treatment, and monthly for 3 months following treatment to assess if there is persistence of infection in cultures. Safety measures will include monitoring of arterial oxygen saturation and methemoglobin levels. All serious and non-serious adverse events will be collected |
| **Assessments** | • Feasibility: ability to recruit subjects, ability to complete the planned treatment, and assessment of their experience and willingness to undergo this therapy<br>• Efficacy: sputum cultures (mycobacteria), symptom scores (cough, quality of life)<br>• Safety: AEs, clinical monitoring assessments (pulse oximetry), vital signs, and physical examinations |
| **Statistical Analyses** | Data will be summarized descriptively for each subject. The overall response rates (culture conversion short and long term) will be calculated after each patient has completed the trial, and exact binomial confidence intervals will be constructed. |

# 3 SCHEDULE OF ASSESSMENTS

Table 3-1: Schedule of Assessments

| | Screening | Treatment Period | | | | | | | | | Follow up Period | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit** | **S** | **A1** | **A2-4** | **A5** | **B1** | **B2-4** | **B5** | **C1** | **C1-4** | **C5** | **F1** | **F2** | **F3** |
| **Day** | **-28--14** | **1** | **2-4** | **5** | **8** | **9-11** | **12** | **15** | **16-18** | **19** | **W7** | **W11** | **W15** |
| Informed consent | x | | | | | | | | | | | | |
| Medical history | x | | | | | | | | | | | | |
| Demographics[a] | x | | | | | | | | | | | | |
| Physical examination | x | x | | | x | | | x | | | x | x | x |
| Height and weight | x | | | | x | | | x | | | x | x | x |
| Vital signs | x | x | x | x | x | x | x | x | x | x | x | x | x |
| Symptom score[b] | x | | | x | | | x | | | x | x | x | x |
| Safety labs[c] | x | | | | | | | | | x | | | |
| CRP | x | | | | | | | | | x | | | |
| Spirometry[d] | x | x[d] | | | x[d] | | | x[d] | | | | | |
| Sputum cultures[e] | x | | | x | | | x | | | x | x | x | x |
| Echocardiogram | x | | | | | | | | | | | | |
| Pulse oximetry | x | x | x | x | x | x | x | x | x | x | x | x | x |
| MetHb measurement | x | x | x | x | x | x | x | x | x | x | | | |
| gNO dosing | | x | x | x | x | x | x | x | x | x | | | |
| Adverse events | | x | x | x | x | x | x | x | x | x | x | x | x |
| Concomitant medications | x | x | x | x | x | x | x | x | x | x | x | x | x |

[a] Demographics include sex, race, and age. Baseline characteristics include diagnosis, and if CF include *CFTR* genotype

[b] Symptom scores will include cough score (Leicester), quality of life (SGRQ, CFQ-R, QOL-B), as appropriate for the underlying diagnosis (i.e. CF subjects will complete the CFQ-R and SGRQ; other subjects will complete the QOL-B and SGRQ)

[c] Safety labs include comprehensive metabolic panel (to include creatinine, AST, ALP, ALT and chemistry), complete blood cell count with differential, GGT, PT/INR, 6-GPD level, and urine pregnancy test (if applicable)

[d] Spirometry will be performed pre and post first treatment of the day

[e] Sputum will be tested for bacteria and mycobacteria (including AFB smear and culture). Susceptibility testing will not be performed

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## List of Tables

# 5 LIST OF ABBREVIATIONS

| Abbreviation | Definition |
|---|---|
| AE | Adverse events |
| ALP | Alkaline Phosphatase |
| ALT | Alanine transaminase |
| AST | Aspartate transaminase |
| ATS | American Thoracic Society |
| BCG | Bacillus Calmette-Guérin |
| CF | cystic fibrosis |
| CFF | Cystic Fibrosis Foundation |
| CFFPR | Cystic Fibrosis Foundation Patient Registry |
| CFQ-R | Cystic Fibrosis Questionnaire-Revised |
| *CFTR* | CF transmembrane conductance regulator gene |
| CRF | case report form |
| DNA | Deoxyribonucleoside acid |
| ECFS | European Cystic Fibrosis Society |
| EDC | electronic data capture |
| FDA | Food and Drug Association |
| GCP | Good Clinical Practice |
| GGT | Gamma-glutamyl transaminase |
| gNO | Gaseous Nitric Oxide |
| HEENT | Head, eyes, ears, nose and throat |
| HIPAA | Health Insurance Portability and Accountability Act |
| IDSA | Infectious Diseases Society of America |
| IND | Investigational new drug |
| INODD | Inhaled NO Delivery Device |
| INR | International normalized ratio |
| IRB | institutional review board |
| LVEF | Left ventricular ejection fraction |
| Mabs | Mycobacterium abscessus |
| MAC | Mycobacteria avium complex |
| MedDRA | Medical Dictionary for Regulatory Activities |
| metHb | Methemoglobin |
| MUSC | Medical University of South Carolina |
| NO | Nitric oxide |
| $NO_2$ | Nitrogen dioxide |
| $O_2$ | Oxygen |
| NTM | Non-tuberculous mycobacteria |
| NTM-PD | Non-tuberculous mycobacteria pulmonary disease |
| PPM | Parts per million |
| SAE | serious adverse event |
| SaO2 | Arterial oxygen saturation |
| SAP | statistical analysis plan |
| SGRQ | St. Georges Respiratory Questionnaire |
| WHO-DD | World Health Organization Drug Dictionary |

# 6 INTRODUCTION

## Overview of NTM lung disease

Non-tuberculous mycobacteria (NTM) have been identified as a pathogen of increasing importance in patients with cystic fibrosis (CF) [Floto 2016]. The Cystic Fibrosis Foundation Patient Registry (CFFPR) has shown prevalence rates for NTM-positive culture in the US of 12% but with considerable variation among states ranging from 0-28% [Floto 2016; Adjemian 2014]. The NTM most commonly identified in patients with CF are *Mycobacterium avium* complex (MAC) and *M abscessus* complex (Mabs) [Olivier 2003; Sermet-Gaudelus 2003].

NTM are insidious opportunistic organisms that cause lung disease in certain patient populations especially those who have cystic fibrosis (CF) but also in other populations [Honda 2015]. Although NTM could be an innocent resident in airway cultures [Martiniano 2017] there are patients in whom NTM may cause progressive lung damage leading to the diagnosis of NTM pulmonary disease (NTM-PD) [Tomashefski 1996]. There are consensus recommendations from the American Thoracic Society (ATS), infectious Diseases Society of America (IDSA), Cystic Fibrosis Foundation (CFF), and the European Cystic Fibrosis Society (ECFS) to guide clinicians in the diagnosis and management of NTM in patients including those with CF [Floto 2016; Griffith 2007].

Treatment of NTM-PD currently involves a multidrug regimen (often 3 or more antibiotics) for prolonged durations; a frequently cited goal for treatment duration is for one year beyond conversion of cultures to negative [Griffith 2007]. These multidrug regimens have potential for intolerability and toxicity resulting in risk for suboptimal treatment and increased likelihood of antibiotic resistance. In addition, many patients will not achieve culture conversion despite adhering to their treatment regimen. There are few data available in CF patients, but overall culture conversion rates reported for other conditions are 55-65% for MAC [Wallace 1996; Tanaka 1998] and 48-58% for Mabs [Jarand 2011].

It is clear from these observations that current options for NTM-PD treatment are limited in scope and in results. An additional problem for CF patients is that the presence of Mabs in sputum cultures may create an insurmountable hurdle for eventual lung transplantation. Although the CFF/ECFS guidelines clearly state that NTM presence is not an absolute contraindication for lung transplantation [Floto 2016], there are some patients who have been declined for transplant listing because of NTM-PD. [Chalermskulrat 2006; personal communication]. Therefore, there is an urgent need for novel treatment of NTM-PD in patients with and without CF.

## Overview of gNO and Rationale for Study

Recent observations of the antimicrobial effects of inhaled nitric oxide gas (gNO) suggest it may be a serious candidate for inclusion in the treatment regimen of NTM-PD. When NO molecules pass through the bacteria cell wall, they bind available thiols (e.g. glutathione) and cause cell death through a combination of asphyxiation of the electron transport complex, impairment of bacterial defense mechanisms, modification of oxygen and nitrogen radical species and metal ion deamination of its DNA [Schaefer 2006]. In vitro studies have demonstrated that NO possesses antimicrobial activity against a wide variety of bacteria, viruses, helminthes and parasites [Schaefer 2006].

*Safety data*: Animal studies of acute exposure to high concentrations of NO (500-1500 ppm NO) for up to 30 minutes demonstrated no acute pulmonary injury (i.e. there were no

differences in histopathological evaluation between the NO-exposed animals and room air control animals). An FDA reviewer noted that, aside from the effects due to formation of methemoglobin (a known adverse effect of NO), oxidative insult to respiratory epithelia may be low/minimal at 200 ppm.

*Anti-mycobacterial effects*: gNO has been demonstrated to be capable of eradicating *M smegmatis*, a fast-growing mycobacteria [Miller 2007]. In vitro testing of *M smegmatis* (mc2155), *M bovis*- Bacillus Calmette-Guérin (BCG) and *M tuberculosis* (H37Rv) exposed to 160ppm gNO have recently been completed by Miller et al. (unpublished). The gNO was delivered both as a continuous exposure or as an interrupted exposure cycle (30 minutes repeated every 3.5 hours) until all bacteria were eradicated. Initial bacterial concentrations were 6 log10 cfu/mL for all bacteria tested. *M smegmatis* and BCG were more susceptible to gNO and complete cidal effect occurred within 10 hrs of exposure or 1,600ppm-hrs. M tuberculosis required 18 hrs or 2,880ppm-hrs of exposure to achieve complete kill. The control arm of the study was exposed to air while the treatment arm was exposed to 160 ± 5ppm gNO. In each of the experiments the control samples remained viable for the duration of the study. The results of multiple 30 min, 160 ppm gNO exposures of *M smegmatis*, BCG and *M tuberculosis* showed a complete kill of each of the organisms tested was achieved by 96 hrs. These results demonstrate that gNO is capable of eradicating a variety of both fast- and slow-growing mycobacteria. This study suggests that gNO could safely be delivered to humans with potential efficacy in patients with NTM.

*Preliminary human work*: This approach to therapy has undergone typical phase I clinical investigation and there is a current Phase II study of CF subjects (clinicaltrials.gov NCT02498535) evaluating the effects of gNO on bacterial species (i.e. *Pseudomonas aeruginosa, Staphylococcus aureus,* and *Stenotrophomonas maltophilia*). A prospective, single center, open labelled, clinical phase I study exposed eight adult CF patients (2 with Mabs in sputum cultures) to gNO by inhalation for 30 min, three times daily, at a concentration of 160 ppm for two periods of 5 days each [Deppisch 2016]. The primary outcome was safety and no serious drug-related adverse events occurred. Methemoglobin increased in all patients to a maximum of 3.0% after 30 min of treatment, considered an acceptable level. Oxygen saturation did not decrease below 95% in any patient. Secondary endpoints were change of bacterial and or fungal load after completion of the treatment from baseline and change in FEV1 from baseline. The intent-to-treat (ITT) analysis revealed a significant mean reduction of the colony forming units (cfu) of all bacteria, but what was notable was the reduction of *M abscessus* by 5 orders of magnitude.

More recently, two patients with CF with persistent Mabs infection and clinical decline despite antibiotic treatment were treated with compassionate use of gNO given in intermittent periods at 160ppm [Yaacoby-Bianu 2018]. One patient received 72 inhalations over 26 days, while the other received 90 inhalations over 21 days. Both subjects showed significant reduction in estimated colony forming units (CFU/ml) for Mabs (decreased from 7000 to 550 and 3000 to 0, respectively). Clinically the subjects were reported to have improvement in well-being and ease of sputum production, while one patients experienced an increase in lung function.

Finally, there are trials of gNO listed on clinicaltrials.gov. One study is recruiting patients with Mabs for a Phase II study in Israel (NCT03208764) with a primary safety endpoint. Another study is being performed in Canada, which is a safety study of gNO in adults with NTM-PD (HC6-24-c207204).

In sum, there is sufficient preclinical evidence of antimicrobial effect of gNO on NTM. There are compelling reasons to use a gas for treatment as it may get to areas of the lung that will not be reached by antibiotics by either the systemic or inhalation route. Even in poorly ventilated lung units, a 50 minute exposure should be sufficient time for NO to achieve therapeutic levels. There are also sufficient safety data that the proposed exposure should be well tolerated. It is premature to predict how this therapy will be best used, but multiple options could be conceived such as eradication of first infection (especially for Mabs), improving outcomes when used in conjunction with standard antibacterial regimens, shorter durations of treatment regimens, among others. This study proposes to demonstrate that there can, indeed, be a killing effect of NTM as well as assess for how quickly it may return in sputum cultures as these will be key factors in designing subsequent treatment trials.

## 7 STUDY OBJECTIVE

The short term goal of this proposal is a proof-of-concept study in which we will expose patients with NTM lung disease and who have persistently positive sputum cultures to test the feasibility of this therapy in this population as well as the safety and efficacy of the therapy.

## 8 STUDY ENDPOINTS

- The primary measure of efficacy will be sputum culture for mycobacteria converted to negative at completion of treatment.
- Secondary measures of efficacy will include assessment of feasibility of this treatment (i.e. recruitment, completion, and satisfaction), sputum culture results for mycobacteria at 3 months following completion of treatment, and safety and tolerability assessments based on adverse events (AEs) and point of care testing for arterial oxygen saturation and methemoglobin levels.

## 9 STUDY DESIGN

### 9.1 Overview of Study Design

This open-label treatment of NTM lung disease is a proof-of-concept study to assess the efficacy of gNO in reducing the burden of NTM in patients known to have persistently positive sputum cultures. The patients will have documented NTM lung disease and meet inclusion criteria of persistently positive sputum cultures even if on antimicrobial therapy. The study is designed to evaluate the feasibility, efficacy and safety of open-label gNO in this population. Feasibility will be assessed by ease of recruitment and completion of the study, as well as a survey of the subjects' experience with the treatment and their willingness to use this as a therapy. Efficacy will be assessed by the results of sputum cultures for mycobacteria, looking at the short term effect (i.e. conversion to negative while on treatment) as well as the long-term effect (i.e. looking at the duration of culture conversion after treatment). Subjects will undergo sputum cultures at baseline and weekly during treatment, and monthly for 3 months following completion of therapy. Additional measures will include symptom scores of cough and quality of life. Safety will be assessed by monitoring of SaO2 and metHb levels while on treatment. All serious and non-serious adverse events will be collected.

### 9.1.1 Screening

The investigator will review the protocol and obtain informed consent from the subjects prior to the conduct of any study procedures. There will be a review of the medical history and demographic information including underlying diagnosis. For those patients with cystic fibrosis (CF) the results of previous genetic testing will be recorded. Physical examination, including vital signs, height and weight, and pulse oximetry, will be performed. Assessment of baseline measures for efficacy will be performed (i.e. sputum collection for mycobacterial culture, cough score (Leicester), quality of life (SGRQ, CFQ-R, QOL-B).

### 9.1.2 Treatment Period (Days 1-15)

The treatment period is separated over 3 weeks (A, B, and C) each with 5 days of treatment, and 2 days off treatment in between. On the first day of each treatment week (A1, B1, C1) subjects will be evaluated for any changes in health or medications. They will undergo physical examination, including height and weight. They will undergo measurement of efficacy outcomes (symptom scores) as per the Study Assessment Schedule (Table 3-1). During each day of treatment (A1-A5, B1-B5, and C1-C5), subjects will be exposed to gNO through a tight-fitting mask at 160 ppm for 50 minutes for each treatment. There will be three treatments given on each day, with 3 hours between each treatment. The subjects will be monitored with pulse oximetry throughout their exposure to gNO to assess SaO2 and metHb levels. On the last day of each treatment period (A5, B5, C5), the subjects will repeat their symptom scores as well as provide sputum for mycobacterial culture.

### 9.1.3 Follow Up Period (3 months)

Patients will be evaluated monthly for 3 months for any changes in health or medications. They will undergo physical examination, including height and weight. They will undergo measurement of efficacy outcomes (symptom scores, sputum cultures) as per the Study Assessment Schedule (Table 3-1).

## 9.2 Rationale for Study Design

This is a proof-of-concept study based upon *in vitro* exposure of NTM to gNO. The primary efficacy measure (conversion to negative mycobacterial cultures) are expected to change in the short term (i.e. during the 3 week treatment period), but assessment after completion of treatment is important to determine if there is a return to culture positivity in the immediate term post-treatment. The overall culture response rate and the time to recurrence (if it recurs) will be important data to determine if this therapy has clinical potential for this patient population and the resulting data will be helpful for estimating the effect size to be used in designing a future randomized controlled trial

The other key measures include reduction in the mycobacterial density (in the event that cultures do not convert to negative, this will provide information about some treatment effect), efficacy based on symptoms, safety, and the feasibility of conducting a larger trial or whether this therapeutic regimen would have viability.

As this is a proof-of-concept study, there is no value to a blinded aspect for the study.

Treatment will be open-label and clinical outcomes will be assessed by the individuals.

# 10 SELECTION OF STUDY POPULATION

## 10.1 Inclusion Criteria

Patients with NTM lung disease who persistently demonstrate infection with positive sputum cultures will be eligible for the study. This will include patients with and without CF as this is typical of the NTM population and this therapy should be non-discriminatory. Inclusion criteria are as follows:

- Subjects are ≥18 years of age and able to provide informed consent.
- Subjects have NTM lung disease as defined by each of the following:
  - Sputum cultures positive for NTM (MAC or *M abscessus*)
  - Radiologic studies that demonstrate features consistent with disease such as nodular bronchiectasis and/or cavities
  - Symptoms consistent with disease including respiratory (e.g. cough, sputum production, hemoptysis, chest pain) and constitutional (e.g. fevers, night sweats, fatigue, myalgias, arthralgias, weight loss)
- Subjects are able to produce sputum for culture (either spontaneous or induced).
- Subjects have a history of persistently positive sputum cultures for NTM defined as
  - ≥ 2 positive cultures over the preceding 6 months AND
  - Has not met the definition for culture clearance in the last 6 months (three negatives in a row)
- Clinically stable with no significant changes in health status within 14 days prior to Screening or Day 1
- Subjects are willing and able to perform requirements of the study.

Appendix: Guidance for eligibility based on definition of persistent infection

The definition of persistent infection in the inclusion criteria is:

- Subjects are able to produce sputum for culture (either spontaneous or induced).
- Subjects have a history of persistently positive sputum cultures for NTM defined as:
    - ≥2 positive cultures over the preceding 6 months AND
    - Has not met the definition for culture clearance in the last 6 months (three negatives in a row.

Since there will be heterogeneity in culture frequency, this table will assist in defining eligibility:

| Samples taken | Samples found to have NTM (positive samples) | | | | | | |
|---|---|---|---|---|---|---|---|
| | 0 | 1 | 2 | 3 | 4 | 5 | 6 |
| 2 | 0/2 | 1/2 | 2/2 | -- | -- | -- | -- |
| 3 | 0/3 | 1/3 | 2/3 | 3/3 | -- | -- | -- |
| 4 | 0/4 | 1/4 | 2/4 | 3/4 | 4/4 | -- | -- |
| 5 | 0/5 | 1/5 | 2/5 | 3/5 | 4/5 | 5/5 | -- |
| 6 | 0/6 | 1/6 | 2/6 | 3/6 | 4/6 | 5/6 | 6/6 |

Red = not eligible
Green = eligible
Yellow = potentially eligible (depending on whether culture conversion definition is met)

The definition of culture conversion is at least 3 consecutive negative mycobacterial cultures from respiratory samples, collected at least 4 weeks apart (i.e. no intervening positives). The table below demonstrates the varying possibilities for the potentially eligible subjects from the table above.

| Number positives | Months prior to screening | | | | | | | Eligible |
|---|---|---|---|---|---|---|---|---|
| | 6 | 5 | 4 | 3 | 2 | 1 | 0 | No |
| 2 | X | O | X | O | O | O | . | No |
| 2 | O | X | X | O | O | O | . | No |
| 2 | X | X | O | O | O | O | . | No |
| 2 | O | X | O | O | O | X | . | No |
| 2 | X | O | O | O | O | X | . | No |

NO-NTM

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 2 | X | O | O | O | X | O | . | No |
| 2 | O | O | O | O | X | X | . | No |
| 2 | O | O | O | X | X | O | . | No |
| 2 | O | O | O | X | O | X | . | No |
| | | | | | | | | |
| 3 | X | X | X | O | O | O | . | No |
| 3 | X | X | O | O | O | X | . | No |
| 3 | X | O | O | O | X | X | . | No |
| 3 | O | O | O | X | X | X | . | No |
| | | | | | | | | |
| 2 | X | O | O | X | O | O | X | Yes |
| 2 | O | X | O | X | O | O | X | Yes |
| 2 | O | X | O | O | X | O | X | Yes |
| 2 | O | O | X | X | O | O | X | Yes |
| 2 | O | O | X | O | X | O | X | Yes |
| 2 | O | O | X | O | O | X | X | Yes |

For those deemed ineligible, they may yet become eligible. In the following table, are different scenarios in which could be rescreened or become eligible within a period of time. S2, S3 and S4 indicate that the participant should be screened again after 2, 3, or 4 months. For these participants, no more than one positive culture has occurred since meeting the definition for culture conversion, and more positive cultures will need to occur to meet eligibility requirements. E1 and E2 indicate that the participant will be eligible after 1 or 2 months. For these persons, two qualifying, positive cultures have occurred since evidence of culture conversion.

| Number positives | Months prior to screening | | | | | | |
|---|---|---|---|---|---|---|---|
| | 6 | 5 | 4 | 3 | 2 | 1 | 0 |
| 2 | X | O | X | O | O | O | S4 |
| 2 | O | X | X | O | O | O | S4 |
| 2 | X | X | O | O | O | O | S4 |
| 2 | O | X | O | O | O | X | S3 |
| 2 | X | O | O | O | O | X | S3 |
| 2 | X | O | O | O | X | O | S2 |
| 2 | O | O | O | O | X | X | E2 |
| 2 | O | O | O | X | X | O | E1 |
| 2 | O | O | O | X | O | X | E1 |
| | | | | | | | |
| 3 | X | X | X | O | O | O | S4 |
| 3 | X | X | O | O | O | X | S3 |
| 3 | X | O | O | O | X | X | E2 |
| 3 | O | O | O | X | X | X | E1 |

## 10.2 Exclusion Criteria

Subjects will be excluded if they have any of the following:

- Smoking history in the prior 6 months
- Significant hemoptysis within 30 days prior to screening (>5 ml of blood in one coughing episode or >30 ml of blood in a 24 hour period)
- Forced expiratory volume at one second ($FEV_1$) <40% of predicted
- On supplemental oxygen or SaO2 <90% at screening or Day 1, or within 30 days prior to enrollment.
- Known cardiac (left heart) insufficiency (defined as LVEF <35%) prior to screening
- Known pulmonary hypertension
- Known or suspected hemoglobinopathy
- Initiation of NTM treatment regimen or a change in the regimen was made in the prior 6 months. Subjects on active treatment can be enrolled if they have been on a stable anti-NTM regimen for at least 6 months.
- Initiation of new chronic therapy within 4 weeks prior to screening
- Use of drugs known to increase methemoglobin (see 12.2.7) at screening
- Any of the following abnormal lab values at screening:
    - 6-GPD deficiency
    - Hemoglobin <10g/dl
    - Platelet count <100,000/mm3
    - Prothrombin time international ratio (INR) >1.5
    - Abnormal liver function defined as any two of the following
        - ALT >3x ULN
        - AST >3x ULN
        - ALP >3x ULN
        - GGT >3x ULN
    - Abnormal renal function defined as:
        - Calculated Creatinine Clearance <50 ml (as calculated by Cockcroft/Gault)
- For women of child bearing potential:
    - Positive pregnancy test at screening or
    - Lactating or
    - Unwilling to practice a medically acceptable form of contraception from screening to Day 15 (acceptable forms of contraception: abstinence, hormonal birth control, intrauterine device, or barrier method plus a spermicidal agent)
- Use of an investigational drug within 30 days prior to screening
- Intravenous or oral steroids (>10 mg/d prednisone equivalent) in the 14 days prior to screening
- Any condition that the Investigator believes would interfere with the intent of this study or would make participation not in the best interest of the subject.

# 11 DOSING OF STUDY DRUG

## 11.1 General Dosing Information

Gaseous NO (5000 ppm), delivered with air as carrier to dilute it to 160 ppm, will be administered by inhalation for 50 minutes three times daily on Days 1-5, 8-12, and 15-19. On each day, treatment will be given with a minimum of 3 hours between the end of one treatment and the start of the following treatment. Subjects will receive 160 ppm during each 50 minute inhalation period (daily exposure 400 ppm hours. This will result in a total of 6000 ppm hours of exposure.

## 11.2 Dosing Information

The 5000 ppm nitric oxide source cylinder contains 5000 ppm (0.5% NO) with the balance of the gas being nitrogen. Only 3.2% of the gas the subject inhales will come from the NO cylinder. Therefore, the nitrogen in the NO cylinder will dilute the inspired oxygen in the carrier gas. This will lower the inspired oxygen from 20.9% to 20.3% or the equivalent of standing at approximately700 feet above sea level. Inclusion criteria for subjects include oxygen saturation >90% on room air and the estimated 3.5 torr change in PaO2 is not anticipated to have a significant clinical effect on subject oxygenation. Subjects will be monitored continuously during treatment with a pulse oximeter.

## 11.3 Dosage Administration

Gas cylinders with the study drug (5,000 ppm NO and 99.5% nitrogen) will be labeled with its contents. These cylinders will be D-size cylinders with a CGA626 valve, containing approximately 350 liters of gas.

Subjects will receive the study drug by inhaling through a nasal mask attached to an Inhaled NO Delivery Device (INODD) administration system. The INODD is comprised of three components including an inspiratory flow monitor with a ratio-metric matching NO injector module, an inhaled gas monitoring module, and a gas mixing subject interface and breathing valve. It is a variable inspiratory flow delivery system that instantaneously matches the subject's inspiratory flow with the injected 5000 ppm NO to deliver 160 ppm of nitric oxide independent of inspiratory flow up to 120 LPM, while keeping nitrogen dioxide ≤ 3 ppm. It is a breath-initiated delivery system and the NO will be blended into the inspiratory gas stream only as long as the subject is inhaling and proportional to the inspiratory flow. The analyzer monitors the inhaled nitric oxide, nitrogen dioxide and oxygen concentrations.

A sample pump in the INODD withdraws a low flow (~ 250 mL/min) from the inspiratory circuit to the subject for analysis of NO, $NO_2$ and $O_2$. These analyzers assure that the subject is receiving the correct gas concentration and assures that the oxygen concentration remains in a safe range and that the inspired concentration of $NO_2$ is below the set alarm threshold limit. Should the NO concentration fall outside the targeted range, an operator set alarm will sound. The system will shut off the NO flow should the NO analyzer measure a value that is ≥ 200 ppm In addition, should the $NO_2$ rise above the alarm limit of 3 ppm, an alarm will sound. If the $NO_2$ rises above 5 ppm, the system will alarm as well as shut off the flow of NO to the

circuit.

# 12 ASSESSMENTS

## 12.1 Timing of Assessments

The timing of assessments is shown in Table 3-1.

## 12.2 Clinical Assessments

### 12.2.1 Subject and Disease Characteristics

Demographic information (age, gender, race) will be captured at Screening. Relevant medical history, including history of current disease, other pertinent respiratory history, and information regarding underlying diseases will be recorded at Screening.

### 12.2.2 Physical Examination

A complete physical examination will be performed by a physician (either the principal investigator or a sub-investigator) at Screening. Body systems to be examined include General, Skin, Lymph Nodes, HEENT, Respiratory, Cardiovascular, Gastrointestinal, Neurologic and Muscoskeletal. Qualified staff (e.g. MD, nurse practitioner, registered nurse, physician's assistant) may complete the abbreviated physical exam (General, HEENT, Respiratory, Cardiovascular and Gastrointestinal) at all other visits. After screening, new clinically significant abnormal physical exam findings must be documented as adverse events (AEs) and will be followed by a physician or other qualified staff at the next scheduled visit or as medically indicated.

### 12.2.3 Vital Signs

Heart rate, blood pressure, respiration rate and temperature will be performed and recorded after resting for 5 minutes at Screening and prior to the start of the first treatment on each day of treatment. Heart rate from the pulse oximeter will additionally be measured and recorded every 5 minutes during each treatment.

### 12.2.4 Oxygen Saturation

Oxygen saturation will be measured by pulse oximetry on room air at multiple visits during the study after the subject has been at rest for 5 minutes. Additionally, during each 50 minute inhalation treatment period, measurements will be recorded at 0, 5, 10, 15, 20, 25, 30, 35, 40 and 45 minutes.

### 12.2.5 Methemoglobin

Will be non-invasively measured (and recorded every 5 minutes) using a pulse methemoglobinometer at Screening, Baseline, continuously during each treatment, recorded every 5 minutes during each treatment. For the first treatment, subjects will be monitored in clinic every 30 minutes post-treatment for adverse events related to study drug inhalation and to

ensure MetHb returns to baseline. NOTE: Any Methemoglobin level >5% (absolute) above baseline requires a repeat level to be measured 5 minutes later and the final measurement should be recorded. If methemoglobin is 15% or higher, see section 13.1 for treatment procedures.

Table 12.1 Monitoring before, during and after treatment

| Measurement | Pre-treatment | During treatment | Post-treatment |
|---|---|---|---|
| Vital signs | HR, BP, RR, T prior to first treatment<br>HR, BP, RR prior to each treatment | HR every 5 minutes | HR, BP, RR upon cessation of treatment<br>Repeat at 30 minutes |
| SaO2 | Prior to treatment | Every 5 minutes | Upon cessation of treatment<br>Repeat at 30 minutes |
| Methemoglobin | Prior to treatment | Every 5 minutes | Upon cessation of treatment<br>Repeat every 30 minutes until return to baseline |

### 12.2.6 Prior and Concomitant Medications

Information regarding all medications administered before study enrollment and through the last study visit will be recorded.

### 12.2.7 Excluded concomitant medications

Some medications are known to be capable of inducing methemoglobinemia and are excluded from use in this trial. This list may include:

Chart I – Drugs Capable of Inducing Methemoglobinemia

| | | | |
|---|---|---|---|
| - Acetaminophen | - Anti malaria drugs | - Nitrates | - Nitric oxide |
| - p-Aminosalicylic acid | - Chloroquine | - Ammonium nitrate | - Nitrous oxide |
| - Local anesthetics | - Primaquine | - Silver nitrate | - Piperazine |
| - Benzocaine | - Quinacrine | - Sodium nitrate | - Rifampin |
| - Bupivacaine | - Methylene blue | - Nitroglycerine | - Riluzole |
| - Lidocaine | - Dapsone | - Nitroprusside | - Sulfonamides |
| - Prilocaine | - Phenacetins | - Bismuth subnitrate | - Sulfasalazine |
| - EMLA* | - Phenazopyridine | - Nitrites | - Sulfamethoxazole |
| - Anticonvulsants | - Flutamide | - Amyl nitrate | - Sulfadiazine |
| - Valproic acid | - Hydroxylamine | - Isobutyl nitrate | - Sulfapyridine |
| - Phenytoin | - Oral hypoglycemics | - Nitrofurantoin | - Sulfanilamide |
| | - Metochlopramide | | - Sulfones |

*Eutetic mixture of local anesthetics.

## 12.3 Safety

Study subjects will remain in the research clinic for at least one hour following each treatment, presuming all monitored parameters are acceptable as per Table 12.1

### 12.3.1 Adverse Events

Information regarding occurrence of adverse events will be captured throughout the study. Duration (start and stop dates and times), severity, outcome, treatment and relation to study medication will be documented on the case report form.

### 12.3.2 Safety Monitoring

A Medical Monitor for this study will consist of a single independent monitoring clinician with experience in the treatment and management of patients with pulmonary diseases. Safety data will be monitored on a continual basis throughout the trial. SAEs and important protocol defined medical events will be reviewed in real time throughout the trial. The Medical Monitor will review all SAE reports and important protocol defined medical event reports, and may at any point temporarily stop the study for concerns of subject safety. IND safety reporting to the FDA and the IRB will be according to guidance procedures as delineated in CFR 312.32.

## 12.4 Research Laboratory Assessments

### 12.4.1 Sputum cultures

Sputum will be collected for culture at Screening, and Days 5, 12, and 19 (treatment dates), and Weeks 7, 11 and 15 (follow up). Sputum samples will be processed at the MUSC clinical laboratory, using standard decontamination procedures, fluorochrome microscopy, solid medium culture on a biplate of Middlebrook 7H10 agar with and without antibiotics, and a broth culture (BACTEC 960 [Becton Dickinson, Sparks, MD] or ESP [TREK Diagnostic Systems, Cleveland, OH]). MAC isolates are identified with AccuProbe (Hologic-GenProbe, San Diego, CA).

Semiquantitative AFB smear and culture results for each submitted clinical specimen will be recorded [Wallace 1996]. Briefly, a negative culture exhibits no mycobacterial growth. Cultures will be reported as positive if growth occurs in broth medium only; growth on broth medium plus solid medium cultures with countable colonies will be reported as 0–49 colonies, 1+; solid medium growth with 50–99 colonies, 2+; solid medium growth with 100–199 colonies; 3+, solid medium growth with 200–299 colonies; and 4+, solid medium growth with at least 300 colonies. For data analysis, each culture will be scored as follows: 0, no growth in broth or solid medium; 1, broth medium growth only; 2, countable colonies (<50 colonies) on solid medium; and 3–6, 1+ to 4+ growth on solid medium, respectively.

### 12.5.1 Quality of life measures

Validated instruments will be used for measurement of symptoms and quality of life. Since study subjects may have different underlying conditions, for which there are different quality of life measures, we will use a condition specific measure for each as follows:

- Cystic fibrosis: Cystic fibrosis Questionnaire-Revised (CFQ-R)
- Bronchiectasis: Quality of Life – Bronchiectasis (QOL-B)
- All: St. George's Respiratory Questionnaire (SGR-Q)
- All: Leicester Cough Score

## 13 DISCONTINUATION OR WITHDRAWAL FROM TREATMENT

### 13.1 Discontinuation of a 50 Minute Inhalation Period (note: treatment will not be initiated if threshold values are present beforehand)

A 50 minute inhalation treatment period will be discontinued if the following occurs.

- a change in the blood pressure systolic value ≥ 20 mmHg or an absolute value of ≤ 80 mmHg repeated at 2 minutes
- an oxygen saturation of < 85% and following recheck of sensor placement
- a reduction in oxygen saturation >5% (e.g. 98% to 92%).
- a persistent* increase in heart rate of ≥ 30 from start of a treatment or an absolute value of 150
- a persistent* absolute increase in methemoglobin of more than 5% above the Day 1 baseline value and follo0wing recheck of sensor placement
- a recorded inspired NO2 > 5 ppm during any treatment
- Subjects with methemoglobin of more than 15% should be treated with 100% oxygen. If 20% or greater, subjects should be treated with Methylene Blue (1 to 2 mg/kg intravenously). Repeat in one hour if necessary. Note: Inject intravenously very slowly over a period of several minutes to prevent local high concentration of the compound from producing additional methemoglobin. Large intravenous doses of Methylene Blue may produce nausea, abdominal and precordial pain, dizziness, headache, profuse sweating, mental confusion and the formation of methemoglobin. Also note that methemoglobin cannot be measured by the oximeter after treatment with methylene blue and should be measured by blood values. See package insert for full contraindications and side-effects. Methylene blue is contraindicated in patients who have developed hypersensitivity reactions to it and in severe renal insufficiency. It is relatively contraindicated in G6PD deficient patients as it can cause severe hemolysis and also in patients with Heinz body anemia. In such cases it may be appropriate to treat with intravenous ascorbic acid.

*Persistent means that the value was obtained on a repeated measurement taken 5 minutes following the original measurement.

### 13.2 Withdrawal from study

If a subject experiences any of the following events during the study period, they should be immediately be withdrawn from the study.

Study drug related adverse events:

- Two consecutive inhalation treatment periods with a persistent absolute increase in methemoglobin of more than 5% above the Day 1 baseline value
- Study drug related significant hemoptysis: production of greater than 50 mL blood in a 24 hour period. Note: Standard treatment for significant hemoptysis should include immediate chest x-ray, hematocrit measurement and if frothy sputum present, an evaluation for hemosiderin labeled macrophages.
- Any study drug related adverse event that repeats upon treatment continuation.

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Other withdrawal criteria:

- At the discretion of the subject
- At the discretion of the Investigator, if deemed appropriate, for any reason
- Subjects will also be withdrawn from the study if they have had to discontinue treatment during the 50-minute inhalation period more than twice due to criteria listed in 13.1.

If a subject is withdrawn because of an adverse event, the subject will be followed and treated by the Investigator until the abnormal parameter or symptom has resolved or stabilized.

The adverse events must be followed to resolution and the follow-up evaluations should be performed when the subject has stabilized.

If for any reason a subject does not complete the study, the reason will be entered on the CRF. All subjects are free to withdraw from participation at any time, for any reason, specified or unspecified, and without prejudice. The Investigator must record the reason for the early termination.

## 14 STATISTICAL AND ANALYTICAL PLANS

Data analysis will be performed by the investigator.

### 14.1 Sample Size and Power

Planned enrollment is a minimum of 6 and a maximum of 10 subjects in this study. If a high enough proportion of subjects demonstrate a response (e.g. 5 of 6 or 6 of 8) early on in the trial, we may be able to limit the sample size, since the 95% confidence intervals would indicate a high certainty that this therapy is worth pursuing in a larger randomized controlled trial. If, however, none of the 10 subjects exhibit a response, then we can be almost certain that this particular therapy is futile, since the resulting 95% confidence interval around the response rate would range from 0% to 31%.

### 14.2 Statistical Analyses

Data will be summarized descriptively for each subject. No formal comparative statistical analyses are planned

### 14.3.1 Background Characteristics

#### 14.3.1.1 Subject Disposition

The number of subjects in each disposition category (e.g., enrolled; prematurely discontinued from the study; and completed the study) will be summarized.

#### 14.3.1.2 Demographics and Baseline Characteristics

The following demographic and baseline characteristics will be captured (as appropriate): *CFTR* genotype, sex, race, age, weight, height, BMI, spirometry, SGRQ, CFQ-R, QOL-B, and sputum culture results.

#### 14.3.1.3 Prior and Concomitant Medications

Medications taken during the collection period specified in Section 11 will be summarized by preferred term using the World Health Organization Drug Dictionary (WHO-DD) for the Safety Set as frequency tables in 2 parts:

- Prior medication: medication that started before the first dose of inhaled nitric oxide regardless of when dosing of the medication ended.
- Concomitant medication: medication received at or after the first dose of inhaled nitric oxide, medication that was received before initial dosing of and continued after initial dosing, or medication with missing stop date.

Medications that started before the first dose of inhaled nitric oxide and continued after the first dose of inhaled nitric oxide will be summarized separately as prior medications and concomitant medications, respectively. Medications with a missing start date will be considered to have a start date before the first dose of inhaled nitric oxide.

### 14.3.2 Efficacy Analysis

For the primary analysis, the proportion of subjects with culture conversion (negative) will be recorded. For the secondary analysis the change (absolute change) in semi-quantitative cultures from baseline will be calculated as post-baseline value – baseline value. Exploratory analysis will be the change in time-to-detection as reported in the broth culture system.

### 14.3.3 Safety Analysis

All safety data will be presented in individual subject data listings.

#### 14.3.3.1 Adverse Events

All adverse events with start date on or after enrollment date through the last study visit will be summarized. Adverse events are defined in Section 15.1.1. Adverse event summary tables will include the following:

- all adverse events;
- related (identified as related to inhaled nitric oxide by the investigator) adverse events;
- adverse events leading to treatment discontinuation;
- serious adverse events (SAEs); and
- adverse events by relationship.

Summaries will be presented by MedDRA system organ class and preferred term using frequency counts and percentages. A subject with multiple occurrences of the same adverse event or a continuing adverse event will be counted only once, by relationship.

## 14.4 Interim Analyses

No interim analyses will be performed but safety will be monitored throughout.

# 15 PROCEDURAL, ETHICAL, REGULATORY, AND

# ADMINISTRATIVE CONSIDERATIONS

## 15.1 Adverse Event and Serious Adverse Event Documentation and Reporting

### 15.1.1 Definition of an Adverse Event

For this study, an adverse event is defined as any untoward medical occurrence in a subject during the study, including any newly-occurring event or previous condition that has increased in severity or frequency after the informed consent form is signed.

A subset of adverse events may meet serious criteria. The definition of an SAE and reporting procedures for SAEs are detailed in Section 15.1.2. The definitions below apply to both adverse events and SAEs.

Planned hospital admissions or surgical procedures for an illness or disease that existed before the subject was enrolled in the study are not to be considered adverse events unless the condition deteriorated in an unanticipated manner during the study (e.g., surgery was performed earlier than planned).

### 15.1.2 Definition of a Serious Adverse Event

An SAE is any adverse event that meets any of the following criteria:

- Fatal (death, regardless of cause, that occurs during participation in the study, or occurs after participation in the study and is suspected of being possibly related toinhaled nitric oxide ).
- Life-threatening, such that the subject was at immediate risk of death from the reaction as it occurred.
- Inpatient hospitalization or prolongation of hospitalization, with the exception of planned or elective hospitalization.
- Persistent or significant disability/incapacity (disability is defined as a substantial disruption of a person's ability to conduct normal life functions).
- Congenital anomaly or birth defect.
- Important medical event that, based upon appropriate medical judgment, may jeopardize the subject or may require medical or surgical intervention to prevent 1 of the outcomes listed above (e.g., an allergic bronchospasm requiring intensive treatment in an emergency room or at home).

### 15.1.3 Documentation of Adverse Events

From the time informed consent is signed through the last study visit all adverse events will be collected. The following data should be documented for each adverse event:

- Description of the event
- Classification of "serious" or "not serious"
- Date of first occurrence and date of resolution (if applicable)
- Causal relationship to inhaled nitric oxide exposure
- Action taken

- Outcome
- Concomitant medication or other treatment given

### 15.1.4 Adverse Event Causality

Every effort should be made by the investigator to assess the relationship of the adverse event, if any, to inhaled nitric oxide exposure. Causality should be classified using the categories presented in Table 15-1.

| **Table 15-1 Classification for Adverse Event Causality** | |
|---|---|
| **Classification** | **Definition** |
| **Related** | There is a suspected association between the event and the administration of inhaled nitric oxide , a plausible mechanism for the event to be related to inhaled nitric oxide and causes other than the inhaled nitric oxide have been ruled out, and/or the event re-appeared on re-exposure to inhaled nitric oxide . |
| **Not related** | The event is believed related to an etiology other than theinhaled nitric oxide . (The alternative etiology should be documented in the study subject's medical record) |

### 15.1.5 Adverse Event Outcome

An adverse event should be followed until the investigator has determined and provided the final outcome. The outcome should be classified according to the categories shown in Table 15-2.

| **Table 15-2 Classifications for Outcome of an Adverse Event** | |
|---|---|
| **Classification** | **Definition** |
| **Recovered/Resolved** | Resolution of an adverse event with no residual signs or symptoms |
| **Recovered/Resolved with Sequelae** | Resolution of an adverse event with residual signs or symptoms |
| **Not Recovered/Not resolved (Continuing)** | Either incomplete improvement or no improvement of an adverse event, such that it remains ongoing |
| **Fatal** | Outcome of an adverse event is death. "Fatal" should be used when death is at least possibly related to the adverse event |
| **Unknown** | Outcome of an adverse event is not known (e.g., a subject lost to follow-up). |

### 15.1.6 Reporting Procedure for Adverse Events and Pregnancy

All serious events (as defined in Section 15.1.2) that occur after obtaining informed consent and assent (where applicable) through the last study visit, regardless of causality, will be reported to the MUSC IRB **within 24 hours** of their awareness.

### 15.1.6 Adverse events of special interest

Short-term NO2 exposures, ranging from 30 minutes to 24 hours, are associated with the following adverse respiratory effects: decreased pulmonary function, chronic bronchitis, dyspnea, chest pain, pulmonary edema, cyanosis, tachypnea, tachycardia, which can aggravate existing heart disease, leading to increased hospital admissions and premature death. We will monitor for and record the following adverse events of special interest: methemoglobinemia, acute hypoxia and hemoptysis, bronchospasm, nasal congestion, sinus congestion, sinusitis, cough, bronchitis, pneumonitis, and alveolitis, as well as nausea, vomiting and diarrhea.

## 15.2 Administrative Requirements

### 15.2.1 Ethical Considerations

The study will be conducted in accordance with the ethical principles founded in the Declaration of Helsinki, and according to local applicable laws and regulations. The institutional review board (IRB) will review all appropriate study documentation to safeguard the rights, safety, and well-being of the subjects..

### 15.2.2 Subject Information and Informed Consent

Subjects must also be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice to their current or future care. Documentation of the discussion and the date of informed consent must be recorded in the subject's medical record or a study/clinic chart. Once all of their questions have been answered and they have voluntarily agreed to participate in the study, each subject will be asked to sign and date the ICF. Informed consent must be obtained from each subject before the performance of any study-related activity.

### 15.2.3 Investigator Compliance

No modifications to the protocol should be made without the approval of the IRB, except where the modification is necessary to eliminate an apparent immediate hazard to human subjects. Any departures from protocol must be fully documented in the source documentation and in a protocol deviation log.

### 15.2.4 Access to Records

The records must also be available for direct inspection, verification, and copying, as required by applicable laws and regulations, by officials of the regulatory health authorities (FDA and others). The investigator must comply with applicable privacy and security laws for use and disclosure of information related to the research set forth in this protocol.

### 15.2.5 Subject Privacy

To maintain subject confidentiality, all case report forms (CRFs), study reports, and communications relating to the study will identify subjects by assigned subject numbers. The FDA (or other regulatory authority) may also request access to all study records, including source documentation, for inspection.

As applicable, in accordance with the Health Insurance Portability and Accountability Act (HIPAA) and associated privacy regulations, a subject authorization to use personally identifiable health information may be required from each subject before research activities begin. This authorization document must clearly specify which parties will have access to a subject's personal health information, for what purpose, and for how long.

### 15.2.6 Record Retention

The investigator will maintain all study records according to GCP guidelines for a minimum of 6 years per MUSC policy.

## 15.3 Data Quality Assurance

The investigator will prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the study for each study participant. Study data for each enrolled subject will be entered into a CRF by site personnel using a secure, electronic data capture (EDC) application (REDCap).[20] Any changes to study data will be made to the CRF and documented in an audit trail, which will be maintained within the study database.

## 15.4 Data Capture

It is the investigator's responsibility to ensure the accuracy, completeness, clarity, and timeliness of the data reported in the subject's CRF. Source documentation supporting the CRF data should indicate the subject's participation in the study and should document the dates and details of study procedures, adverse events, other observations, and subject status.

The investigator will retain the CRF data and corresponding audit trails that show all updates to data, with user identification, date, and time.

## 15.5 Publications and Clinical Study Report

### 15.5.1 Publication of Study Results

Any and all scientific, commercial, and technical information in this protocol or elsewhere should be considered the confidential and proprietary property of the investigator. The investigator will be responsible for publication and/or disclosure of study results.

### 15.5.2 Study Report

A clinical study report will be written by the investigator and submitted to the FDA per IND requirements.

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