

CLINICAL PROTOCOL

#CLA-CC10-02

EFFICACY OF RECOMBINANT HUMAN CLUB (CLARA) CELL 10 KDA PROTEIN (CC10) ADMINISTERED TO PREMATURE NEONATES WITH RESPIRATORY DISTRESS SYNDROME

Sponsor: Therabron Therapeutics, Inc.
(formerly Clarassance, Inc.)
9430 Key West Avenue, #150
Rockville, MD, 20850
Phone: 240-205-7275

Investigators:

Jonathan M. Davis, M.D.
Chief of Newborn Medicine
Department of Newborn Medicine
The Floating Hospital for Children
at Tufts Medical Center
TMC #44
Professor of Pediatrics
Tufts University School of Medicine
750 Washington Street
Boston, MA. 02111
Tel: 617-636-5322
Fax: 617-636-1456
E-mail:jdavis@tuftsmedicalcenter.org

Richard B. Parad, M.D., MPH
Associate Professor of Pediatrics
Harvard Medical School
Co-Director, Clinical and Translational Research
Program
Department of Pediatric Newborn Medicine
Brigham and Women's Hospital
75 Francis Street
CWN RM 418
Boston, MA 02115
Tel: 617-732-7371
Fax: 617-278-6983
Email: rparad@partners.org

Date: updated October 1, 2015

Replaces previous version dated: March 5, 2015 (#CLA-CC10-02)

TABLE OF CONTENTS

| | | |
|-------|---|----|
| 1 | GENERAL INFORMATION..... | 4 |
| 1.1 | Investigators and Study Sites..... | 4 |
| 1.2 | Independent Safety Monitoring Committee..... | 4 |
| 1.3 | Sponsor..... | 4 |
| 2 | BACKGROUND INFORMATION..... | 4 |
| 2.1 | Indication to be Studied..... | 4 |
| 2.2 | Study Drug | 5 |
| 2.3 | Rationale for the Clinical Study..... | 6 |
| 2.4 | Non-Clinical Studies: Pharmacology and Toxicology Studies | 6 |
| 2.5 | Previous Human Experience | 8 |
| 2.5.1 | Previous Clinical Trials | 8 |
| 2.5.2 | Non-Therapeutic Studies of Human CC10 Physiology | 9 |
| 2.6 | Potential Risks | 9 |
| 3 | OBJECTIVES OF THE STUDY | 10 |
| 4 | STUDY DESIGN..... | 10 |
| | Table 1: Treatment groups for IT rhCC10 Administration..... | 10 |
| 5 | SELECTION, ENROLLMENT & WITHDRAWAL OF STUDY SUBJECTS | 11 |
| 5.1 | Inclusion Criteria..... | 11 |
| 5.2 | Exclusion Criteria | 12 |
| 5.3 | Randomization..... | 12 |
| 5.4 | Withdrawal Criteria..... | 13 |
| 6 | TREATMENT PLAN | 14 |
| 6.1 | Baseline Examination | 14 |
| 6.2 | Surfactant Administration..... | 14 |
| 6.3 | Study Drug Administration | 14 |
| 6.4 | Subsequent Examinations | 14 |
| | Table 2: Schedule of EVALUATIONS..... | 15 |
| | Table 3: Schedule of Evaluations (Period 2)..... | 16 |

| | | |
|-------------|---|----|
| 6.5 | Monitoring and Management of NEC..... | 17 |
| 6.6 | Longer-Term Patient Follow-Up..... | 17 |
| 6.7 | Procedure for Collection of Blood Samples | 18 |
| 6.8 | Analysis of Samples | 19 |
| 6.9 | Concomitant Medications..... | 19 |
| 7 | ADVERSE EVENTS | 20 |
| 7.1 | Serious, Life-Threatening or Unexpected Adverse Events | 20 |
| 7.2 | Reporting of Serious, Life-Threatening or Unexpected Adverse Events | 21 |
| 7.3 | Serious Adverse Event Reporting | 21 |
| 7.4 | Additional Adverse Event Reporting | 21 |
| 7.5 | Criteria for Suspension of the Trial (Stopping Rules)..... | 22 |
| 8 | EXPLORATORY ENDPOINTS | 23 |
| 8.1 | Primary Endpoint: Long Term Efficacy – 12 months | 23 |
| 8.2 | Secondary Endpoints: Long Term Efficacy – 6 & 18 months..... | 23 |
| 8.3 | Secondary Endpoints: Short Term Efficacy | 23 |
| 8.4 | Secondary Endpoints: Safety and Efficacy - Adverse Events | 24 |
| 8.5 | Statistical Considerations..... | 25 |
| 9 | ETHICAL CONSIDERATIONS | 26 |
| 9.1 | Informed Consent..... | 26 |
| 9.2 | Institutional Review Boards | 26 |
| 10 | DATA HANDLING, ANALYSIS AND RECORD KEEPING | 27 |
| APPENDIX A: | DEFINITIONS OF SPECIFIC ADVERSE EVENTS | 28 |
| APPENDIX B: | INFORMED CONSENT FORMS | 32 |
| APPENDIX C: | NICU DISCHARGE INTERVIEW | 33 |
| APPENDIX D: | POST-DISCHARGE VISITS..... | 34 |
| APPENDIX E: | MONTHLY PATIENT SYMPTOM DIARY CARD | 35 |
| APPENDIX F: | MONTHLY PATIENT QUANTITATIVE DIARY CARD..... | 36 |

1 GENERAL INFORMATION

1.1 Investigators and Study Sites

The study will be conducted at two sites: the Floating Hospital for Children, Tufts Medical Center, Boston, MA and Harvard Medical School (Brigham & Women's Hospital), Boston, MA. Names and addresses of the Principal Investigators are as follows:

- Jonathan M. Davis, M.D., Professor of Pediatrics, Tufts University School of Medicine, The Floating Hospital for Children, TMC #44, 750 Washington Street, Boston, MA, 02111.
- Richard B. Parad, M.D., M.P.H., Associate Professor of Pediatrics, Harvard Medical School, Brigham and Women's Hospital, 75 Francis Street, CWN RM 418, Boston, MA, 02115.

1.2 Independent Safety Monitoring Committee

Safety of the study will be monitored on an ongoing basis by an independent data, safety monitoring board (DSMB) consisting of two senior Neonatologists, a biostatistician, and a pediatric pulmonologist with significant experience in multicenter clinical trials. The DSMB will promptly receive information on all adverse experiences and will have final authority to terminate enrollment in the study if deemed necessary (see stopping rules). The randomization code for the study will be provided to the DSMB if requested; otherwise the DSMB will remain blinded.

1.3 Sponsor

The Sponsor is Therabron Therapeutics, Inc., 9430 Key West Avenue, Rockville, MD 20850, Phone: 240-205-7275 The Medical Monitor for the study is Dr. Lisa Beth Ferstenberg, M.D., who is Chief Medical Officer for the Sponsor.

2 BACKGROUND INFORMATION

2.1 Indication to be Studied

The purpose of the present study is to evaluate the efficacy of a single intratracheal (IT) dose of rhCC10 to intubated premature infants receiving positive pressure ventilation for treatment of respiratory distress syndrome (RDS) to prevent long term respiratory complications referred to as chronic respiratory morbidity (CRM; asthma, cough, wheezing, multiple respiratory infections). Traditionally, short term predictors of CRM have involved the diagnosis of bronchopulmonary dysplasia (BPD). However, the clinical definition of BPD has changed several times over the past decade. The current consensus method for determining BPD is assessing oxygen requirements at 36 weeks corrected gestational age (CGA) using a target oxygen saturation range of 88-94% or through oxygen

challenge testing. However a cohort of premature infants followed to 18-22 months CGA demonstrated that this definition correctly predicted CRM only 35-40% of the time, although accuracy increased as the severity of BPD worsened. A major problem for investigators studying BPD is that premature infants who do not develop BPD can also suffer CRM and have lung function abnormalities at follow-up. In view of these significant methodologic difficulties, the American Academy of Pediatrics, the NIH and FDA have recommended that clinical trials should evaluate CRM in the first 1-2 years of life as a potentially more meaningful outcome.

Extremely low gestational age infants (ELGANs) with RDS are at particular risk of developing BPD, a condition associated with marked inflammation, injury to small airways, and arrest of alveolarization that is believed to result in CRM. BPD is associated with significant morbidity (asthma, repeated pulmonary infections, re-hospitalizations) and mortality, and affects up to 15,000 infants in the US annually. The lungs of premature infants are deficient in factors that regulate inflammatory responses (including CC10). This is critically important since intrauterine infection and inflammation are believed to be involved in the pathogenesis of preterm delivery as well as acute and chronic lung injury. These factors are normally present in the term lung in preparation for the transition to the extrauterine environment. RDS and the associated immature lung structure require rescue with exogenous surfactant and support with supplemental oxygen and positive pressure mechanical ventilation, which amplifies lung inflammation, injury, fibrosis, and impaired lung development.

2.2 Study Drug

The study drug, rhCC10, is a recombinant version of natural human CC10 protein. Native CC10 is produced primarily by non-ciliated respiratory epithelial cells, called Club (Clara) cells and is the most abundant protein in the mucosal fluids in normal healthy lungs. CC10 circulates in the blood and is excreted in the urine. The recombinant version is nearly identical to the native protein and shares all biological properties with the native protein that have been characterized thus far. rhCC10 is produced in *E. coli* bacteria.

The rhCC10 drug formulation to be used in this study is a clear, colorless liquid formulated in unbuffered normal saline (0.9%) at a concentration of 5.5 mg/ml. It is aliquoted into sterile septum-capped, 2 ml glass vials and stored at 4°C. rhCC10 is stable under these conditions for at least 14 years and stable at room temperature for at least 18 months. This formulation has been administered by IT instillation in premature infants and by intranasal instillation in healthy adults.

Drug administration: In the previous pilot clinical trial in premature infants, a single dose (1.5 and 5 mg/kg/dose) of rhCC10 was administered by IT instillation within 24 hours of birth in intubated premature infants treated for surfactant deficiency. In the present study, administration of rhCC10 will

be nearly identical to the first clinical trial, however, in the present study the administration of study medication to each lung will be specifically instilled over not less than a 30 second period (duration of instillation not specified in first trial). In addition, just prior to instillation, adjust ventilator settings as follows:

- Increase PIP by 1-2 cm H₂O
- Increase the rate to 35 (if not already there)
- Increase FiO₂ by 5-10%

Dose selection: The IT dose will replicate the single IT doses of 1.5 mg/kg and 5.0 mg/kg from the previous clinical study. Doses will be calculated based on the patient's birth weight.)

2.3 Rationale for the Clinical Study

BPD is a disorder characterized by marked inflammation and alveolar hypoplasia, affecting 20-60% of extremely low birth weight preterm infants. It is associated with significant mortality and short- and long-term morbidity. Long-term morbidities include CRM such as asthma and repeated respiratory tract infections during infancy that lead to increased hospitalizations and treatments with asthma medications. Abnormal neurodevelopmental outcomes, retinopathy of prematurity (ROP), and other significant morbidities of prematurity occur at increased frequency in infants with BPD. While exogenous surfactant therapy has reduced the overall severity of BPD, the prevalence of BPD has increased with improved survival of these infants. New treatments to prevent BPD and subsequent CRM are urgently needed.

There is ample rationale for studying CC10 supplementation in these patients. The phenotypes of two different strains of CC10 knockout mice indicate that CC10 is an autocrine factor required for the normal development of non-ciliated airway epithelial cells, including Club (Clara) cells. CC10 regulates inflammatory responses and protects the structural integrity of pulmonary tissue while preserving pulmonary mechanical function during various insults (e.g. viral infection, bacterial endotoxin, ozone, allergens, hyperoxia). Together these properties suggest that administration of rhCC10 may help to facilitate development of normal airway epithelia and prevent the inflammation that leads to CRM in these infants.

2.4 Non-Clinical Studies: Pharmacology and Toxicology Studies

Native CC10 is produced primarily by non-ciliated respiratory epithelial cells and is the most abundant protein in normal adult lungs, constituting up to 7% of the total extracellular protein. Native CC10 is synthesized by a number of tissues including the lungs, pancreas, uterine endometrium, prostate, and seminal vesicles. The normal physiological tissue distribution for CC10 includes all

mucosal tissues except the eyes and central nervous system. The concentration of endogenous CC10 in the blood ranges from 10-120 ng/ml in normal, healthy adults and up to 5 µg/ml in patients with renal dysfunction. From the blood, CC10 enters numerous tissues and organs and is also excreted in the urine. Several studies have found significantly lower endogenous CC10 protein concentration and expression in the lungs of preterm infants who died or developed severe BPD, suggesting an integral role of this protein in normal lung homeostasis.

The CC10 protein has potent anti-inflammatory and anti-fibrotic properties as demonstrated by numerous *in vitro* and *in vivo* studies. Although there is no consensus as to the central mechanism of action, CC10 may mediate many of its short term anti-inflammatory effects through its role in vesicle and protein trafficking in Club (Clara) cells. Respiratory epithelial cells in CC10 knockout mice demonstrate a lack of secretory vesicles and the presence of unusual intracellular structures characterized by multi-layer stacked membranes and disproportionate amounts of Golgi, rough endoplasmic reticulum, and lysosomal compartments compared to respiratory epithelial cells from non-knockout mice. In the longer term, CC10 may mediate effects through development and/or maintenance of airway epithelial cells, including Club (Clara) cells (autocrine function), which secrete the majority of native CC10 in the lungs and circulation.

rhCC10 follows the natural physiological distribution path for the native protein from lung to blood and blood to urine. The circulating half-life of rhCC10 is 2-2.5 hours, which is prolonged to 9-11 hours by an uptake phase when administered to a mucosal surface (intratracheal instillation). The circulating half-life decreases slightly with increasing dose, suggesting active clearance of the protein. Although all tissues and organs are exposed to CC10, tissues that primarily take up excess rhCC10 include the lungs (airways and alveoli), esophagus, and thyroid. Not only is excess circulating rhCC10 taken up specifically by the lungs, but also small amounts of protein actually reach the extracellular mucosal fluid where it is detected in tracheal aspirate fluid (TAF) and bronchoalveolar lavage fluid (BAL).

Several toxicology studies have been conducted with no evidence of acute or chronic toxicity or any significant tissue pathology, including IT administration in newborn piglets (n=86), premature lambs (n=22), premature baboons (n=4), and juvenile rabbits (n=18). No evidence of acute or chronic toxicity was observed in adult cynomolgus monkeys that received seven daily intranasal doses of rhCC10. No evidence of acute or chronic toxicity was observed in juvenile rats that received 14 daily IV doses of rhCC10. Several models of acute lung injury and infection (RSV, influenza) have demonstrated the protective effects of rhCC10 (by different routes of administration) without evidence of toxicity.

2.5 Previous Human Experience

2.5.1 Previous Clinical Trials

Two Phase 1/2 clinical trials have been conducted with rhCC10. Both studies indicated that rhCC10 appeared to be safe and well-tolerated. rhCC10 demonstrated potent anti-inflammatory activity and longer term benefits in patients who were deficient in native CC10.

The first trial was performed in premature infants with RDS, in which a single dose of rhCC10 was administered by IT instillation. Two dose levels of rhCC10 (1.5 mg/kg and 5 mg/kg) were evaluated in a randomized, double-blinded, placebo-controlled, dose-escalation design, conducted at 3 clinical centers in the US. A total of 22 infants were enrolled in three groups including placebo (n = 7), low dose (n = 8), and high dose (n = 7). Two infants in the study died. The first had received 1.5 mg/kg of rhCC10 and died of complications of necrotizing enterocolitis (NEC). The second had received 5 mg/kg of rhCC10 and died of complications from respiratory failure. Neither death was deemed to be attributable to the study drug. Significant reductions in total protein content, neutrophil counts, and total cell counts were observed in TAF in rhCC10-treated infants compared to placebo controls (unusual in this small a study population). At the six month CGA follow up, data were collected for a total of 17 patients on measures of CRM (one infant from each experimental group was lost to follow up). Interestingly, none of the CC10-infants (0/11) had been re-hospitalized for respiratory causes following NICU discharge, while 50% (3/6) of the placebo infants had been re-hospitalized for respiratory causes. The prevention of acute inflammation and preservation of normal airway and alveolar development may contribute to this long term benefit. No anti-rhCC10 antibodies were detected in sera collected from all infants at 28 days of life.

The second trial was performed in healthy adults with seasonal allergies in which rhCC10 was administered by intranasal instillation (1.1 mg per day for seven consecutive days). The study was a placebo-controlled, double-blinded, cross-over design at a single center in Sweden. Patients were previously characterized with allergies to tree pollen but were otherwise healthy. Each subject was given a daily intranasal instillation of rhCC10 immediately prior to receiving an intranasal instillation of allergen. This nasal allergen challenge (NAC) causes a mild inflammatory response in the nasal epithelia. Total nasal symptoms scores (TNSS) were documented within 30 minutes of each challenge. Repeat intranasal administration of rhCC10 did not affect TNSS in this model, but also raised no safety or tolerability concerns. No blood was taken in this study and it is not clear whether intranasal dosing resulted in systemic exposure.

2.5.2 Non-Therapeutic Studies of Human CC10 Physiology

Several studies have examined the concentrations of endogenous CC10 in premature newborn infants and found that CC10 concentration in pulmonary fluids is directly proportional to gestational age. A variety of methods have been used to detect and measure native CC10 in these studies including radioimmunoassay, ELISA, and LC-mass spectrometry. The consensus findings are that pulmonary CC10 expression and protein levels in lung fluids are low in ELGANS and increase over time with increasing gestational age. Rapid increases in CC10 levels in TAF occur following premature birth. No studies have been performed to document CC10 TAF levels in term infants with normal lungs. One study documented that CC10 mRNA is detectable in human fetal lungs as early as week 16, with the protein becoming detectable in amniotic fluid around week 22, and rapidly increasing after week 28 then plateauing at week 32 (~ 1 µg/ml; a pattern similar to surfactant proteins). Another study showed that CC10 levels are lowest in preterm infants who die or develop BPD compared to those who do not, and that a greater proportion of the native CC10 in patients who die or develop BPD is oxidized. It is notable that CC10 is also produced by the uterine endometrium and the placenta during the first and second trimesters of pregnancy, such that the fetus is exposed to CC10 throughout pregnancy and before the fetal lungs start producing it.

2.6 Potential Risks

Human CC10 is a natural product of respiratory epithelia and is normally present in the extracellular fluid of the lung, as well as amniotic fluid. The clinical protocol proposes to supplement low endogenous CC10 levels in the lungs of premature neonates with a recombinant human protein. Thus, we do not expect immunogenicity to be a problem. Peak concentrations of rhCC10 in lung fluid and blood of infants to be treated may exceed normal adult levels, but should be well within the ranges explored in non-clinical pharmacology and toxicology studies. rhCC10 has been tested in non-clinical toxicology studies at doses up to 25 mg/kg (IT) and 2 mg/kg (IV).

CC10 is transcriptionally upregulated in the lungs by corticosteroids. Therefore, patterns of toxicity secondary to excessive CC10 that could occur secondary to treatment with corticosteroids were specifically examined in the first study in preterm infants and in all animal pharm/tox studies. Although no such toxicities have been detected, these effects will continue to be monitored closely in the present studies.

The pharmacokinetic analysis of CC10 in TAF fluids in the first trial demonstrated a trend that native CC10 expression was higher in day 3 TAF of placebo infants than in CC10-treated infants. Although the number of day 3 TAF samples was extremely limited (n=2-3/group due to many infants

being extubated), there is a possibility that administration of exogenous rhCC10 may transiently suppress expression of the native protein in the lungs. This will be closely monitored during the present trial.

There was a higher incidence of confirmed (n=3) and suspected (e.g. radiologic; n=5) NEC in rhCC10-treated infants compared to the placebo group (P=NS). This was not thought to be due to administration of study drug, since the NEC occurred 3-6 weeks after rhCC10 administration and because other infants in the NICU who were not enrolled in the study also developed NEC at the same time. (NEC is known to occur in clusters). However, the incidence and severity of NEC, as well as other infectious related AEs (e.g. sepsis, pneumonia, etc.) will be closely monitored during this study.

3 OBJECTIVES OF THE STUDY

The purpose of the placebo-controlled study is to determine the efficacy of a single IT dose of rhCC10 (1.5 and 5 mg/kg in a 2 ml/kg fixed volume) in improving survival without CRM as indicated by a reduction in respiratory complications 12 months CGA (using validated respiratory diaries and pulmonary questionnaires, see Appendices D, E, and F). Based on these data, future studies will be designed to determine whether administration of rhCC10 to neonates with RDS is effective in improving survival without CRM.

4 STUDY DESIGN

This study is designed as a randomized, blinded, placebo-controlled phase 2 trial. The study will enroll premature infants with a gestational age of 24-29 weeks who are receiving positive pressure mechanical ventilation and surfactant replacement therapy for treatment of RDS. Placebo (normal saline) will be compared to two dose groups of rhCC10 as shown in Table 1:

TABLE 1: TREATMENT GROUPS FOR IT RHCC10 ADMINISTRATION

| Treatment | Route of Administration | Number of doses | Intratracheal Dose level |
|------------------|-------------------------|--------------------|--------------------------|
| Placebo (n = 44) | Intratracheal | 1, on day of birth | n/a |
| rhCC10 (n = 22) | Intratracheal | 1, on day of birth | 1.5 mg/kg |
| rhCC10 (n = 22) | Intratracheal | 1, on day of birth | 5 mg/kg |

The clinical study has a blinded, placebo-controlled design. The purpose of blinding the study is to minimize treatment bias while randomization offers each infant the possibility of receiving the study drug.

A total of 88 patients will be enrolled in three treatment groups in which high and low dose rhCC10 will be compared to placebo. A total of 44 patients will receive placebo, 22 patients will receive 1.5 mg/kg rhCC10, and 22 patients will receive 5 mg/kg rhCC10. Complete results of the study should allow direct comparison of three groups.

Patients enrolled in the study will meet the prescribing criteria for *Survanta* or *Curosurf* and will receive the usual recommended clinical dose of surfactant replacement therapy. Each patient will then receive a single IT dose of the study drug (or placebo) within four hours after surfactant. Patients may be given subsequent doses of surfactant if required, but will not receive additional doses of rhCC10.

Concentrations of rhCC10 will be evaluated in serum derived from the infant, umbilical cord, or placental blood before drug administration and in serum or plasma and urine on days 1 and 28, and 12 months CGA. TAF will be obtained on similar days if the infant is still intubated to evaluate the effects of a single IT dose of rhCC10 on native CC10 expression in the lungs. Total protein, TH2 cytokines, IL-6, and cellular infiltrates will also be evaluated in TAF samples, to the extent permitted by the volume of patient samples collected.

5 SELECTION, ENROLLMENT & WITHDRAWAL OF STUDY SUBJECTS

5.1 Inclusion Criteria

Newborn infants will be considered for the study if the following criteria are met:

- Age \leq 24 hours;
- Birthweight between 600 and 1,250 grams;
- Gestational age 24-29 weeks (not less than 24 weeks); at birth based on best estimate using obstetrical sonography (first or second trimester), solid dating criteria, or Ballard examination;
- Birthweight appropriate for gestational age;
- 5 minute Apgar score >5 (ie. 6-10);
- Diagnosis of neonatal RDS based on clinical and/or radiographic criteria;
- Requiring intubation and mechanical ventilation for treatment of RDS;
- Received at least one dose of surfactant (prophylaxis or rescue) or the decision to treat with surfactant has already been made (e.g. infant is intubated or in the process of being intubated and/or surfactant has been prescribed); and
- Written informed consent is obtained from the infant's parent or legal guardian prior to enrollment of the patient and agrees to all study-related procedures and evaluations, including those required after hospital discharge.

5.2 Exclusion Criteria

Patients meeting the inclusion criteria will not be eligible for the study if any of the following are present:

- 5 minute Apgar score of ≤ 5 (ie. 1-5); except in cases where the subject's Apgar score is ≤ 5 at 5 minutes, normalizes by 10 minutes, no acidosis is present on cord blood gas and the neonatal depression is thought to be due to maternal anesthesia or other drug exposure such as MgSO₄.
- Major congenital abnormalities (chromosomal, renal, cardiac, hepatic, neurologic, or pulmonary malformations; minor anomalies such as cleft lip/palate are permitted);
- Evidence of severe neonatal depression (as defined by cord blood pH ≤ 7.00 and/or an Apgar score of < 4 at 10 minutes);
- Evidence of congenital infection (bacterial or non-bacterial);
- Requires a major surgical procedure prior to administration of Study drug
- Enrollment in any other study involving administration of another investigational drug;
- Any condition which could preclude receiving study drug or performing any study-related procedures;
- Use of postnatal corticosteroids prior to administration of rhCC10, except as specified in the protocol;
- Use of inhaled nitric oxide prior to administration of rhCC10;
- Mother is known to be seropositive for HIV or HTLV-1 (per maternal medical records);
- Parent or guardian is unable or unwilling to complete the study diary after hospital discharge;
- Parent or guardian is unable to bring the infant back to the study center for follow-up evaluations after discharge.

5.3 Randomization

As previously described, two dose levels will be evaluated against the placebo in two consecutive cohorts. The first cohort will randomize patients to receive either 1.5 mg/kg or placebo. The second cohort will randomize patients to receive either 5 mg/kg or placebo. Each cohort will randomize 44 infants to either placebo or drug treatment. The overall design is 2:1:1; 44 (placebo):22 (1.5 mg/kg):22 (5mg/kg). The randomization scheme was developed and is maintained by StudyTrax, a secured electronic data capture platform that is compliant with 21 CFR-11 and HIPAA. A randomization ID is generated when a subject is randomized using the format TMC-001, BWH-002, and

so on (i.e. 3 letter site designation and three numbers designating the sequence in which the patient was enrolled). The randomization scheme uses the permuted block randomization method, with stratification by site and by gestational age group (divided into 24-27 wks CGA and 27-29 wks CGA), with block sizes 2,2,4. For Cohort 1, treatment groups are: Placebo and 1.5 mg/kg. When Cohort 1 is completed, Cohort 2 treatment groups will be: Placebo and 5.0 mg/kg. Cohort is also listed as a Stratification factor so that when Cohort 2 starts, any open blocks from the first cohort will not be filled. The Cohort is automatically set to 1 at the start of the study. Once Cohort 1 is done and Cohort 2 starts, that will change. Each site's pharmacy will receive authorization to access the patient randomization assignment via the Internet on StudyTrax.

The randomization assignment must not be disclosed to anyone outside the pharmacy. Patients who meet the inclusion criteria and are successfully enrolled will be assigned a patient Randomized ID number. Due to the time critical nature of managing the respiratory support of the subject and dosing with study medication, it is permissible for the patient to be randomized before receiving the first dose of surfactant. The patient Randomization ID number and the birth weight of the patient will then be communicated to the pharmacy on a paper form requesting study medication. The pharmacist will then access the StudyTrax randomization assignment on the Internet. The patient will be assigned to one of the three groups (placebo, low dose or high dose) as appropriate to the cohort, and an opaque syringe containing an appropriate dose of the study drug or placebo will be sent to study personnel in a sealed envelope. In order to administer the study drug within 4 hours of surfactant administration, the patient's birth weight should be communicated to the pharmacy as soon as it is available. The syringe received from the pharmacy will be identified only with the patient Randomization ID number and will contain 1.5 – 3.1 mL of solution, depending on the birth weight of the patient. StudyTrax will hold the key to patient treatment assignments, which will not be disclosed until the end of the study.

Given the small size of the study and the simple randomization scheme, it is possible that a significant discrepancy may exist among the treatment groups in birth weight and/or gestational age. Any such difference will be taken into account in evaluating the results of the study.

5.4 Withdrawal Criteria

A patient may be withdrawn from the study by a parent or legal guardian or by the attending physician at any time.

6 TREATMENT PLAN

6.1 Baseline Examination

Examination prior to administration of the study drug (and preferably prior to surfactant administration) will include at least the following components:

- Physical examination, including determination of body weight;
- APGAR score;
- SNAPPE II score (performed within first 12 hours of life);
- Chest radiograph, if available;
- Blood sample (for electrolytes, liver and renal function tests, CBC with differential and platelets, CC10 concentration); and
- TAF sample taken prior to surfactant administration (if possible) for cell counts and concentrations of CC10, total protein, sIgA, and cytokines.
- Urine sample, if available
- Stool sample, if available

All blood samples for CC10 concentration determinations will be limited to ~200 microliters each of whole blood to be separated to yield serum.

6.2 Surfactant Administration

Survanta or Curosurf will be administered according to the prescribing instructions. Subsequent doses of surfactant may be administered at any time at the discretion of the attending physician.

6.3 Study Drug Administration

The study drug will be administered to patients within four hours after surfactant administration, but no sooner than 30 minutes after surfactant. Just prior to administration of the study drug, the following adjustments to the ventilator settings should be done: increase the PIP by 1-2 cm H₂O, increase the rate to 35 breaths/min (if not already there) and increase FiO₂ by 5-10%. The study drug should be administered IT in two aliquots. Initially, half the dose will be instilled into one lung (via a pre-measured feeding tube placed into the distal third of the endotracheal tube with the patient in a lateral decubitus position and 30° of Trendelenburg), then the second aliquot will be given into the other lung in a similar fashion. The administration of the study medication to each lung will be specifically instilled over not less than a 30 second period. No further study medication will be provided after the first day of life.

6.4 Subsequent Examinations

During the initial 4-week, post-dosing period (28 days), serum, urine, stool, and TAF samples will be taken on days 1 (baseline) and 28. If possible, samples will also be collected on days 7, 14, and

21 only if scavenged blood from clinical specimens is available. Serum and urine samples for CC10 analysis will also be collected on visit 20 (see table 3). TAF samples on day 28 will only be collected if the infant is still intubated.

A schedule of clinical and pharmacological evaluations is shown in Table 2. During the initial active-treatment period, formal study visits and procedures will be performed on a weekly basis. Weekly formal study visits will review concomitant medications, adverse experiences, collection of vital signs, growth parameters (weight, length, head circumference), physical and neurologic examinations, respiratory status (days of mechanical ventilation, days of nasal CPAP, oxygen requirements), nutritional support data and safety laboratories (electrolytes, glucose, calcium, hepatic and renal function, complete blood count with differential). Maternal history including smoking, atopy, and asthma will also be collected. In order to document that initial severity of illness is comparable between groups, a Score for Neonatal Acute Physiology Version II (SNAPPE-II) will be recorded during the initial visit. Cranial sonography to detect intraventricular hemorrhage (IVH) will be performed within 7 ± 2 days of enrollment and to detect periventricular leukomalacia (PVL) within 28 ± 2 days per standard of care for infants of this gestational age.

TABLE 2: SCHEDULE OF EVALUATIONS
(**BOLDED** text Represent Study-Related Procedures)

| Evaluation | Visit 1 | Visit 2 | Visit 3 | Visit 4 | Visit 5 |
|--|--------------------|---------|---------|---------|---------|
| Study day | day 1 ⁵ | day 7 | day 14 | day 21 | day 28 |
| Inclusion/exclusion criteria | X | | | | |
| Informed consent | X | | | | |
| Study drug administration | X | | | | |
| Head ultrasound ² | | X | | | |
| Chest X-ray ² | X | | | | |
| Physical examination/Vital Signs/Anthropomorphics including eye exam | X | X | X | X | X |
| Respiratory and Nutritional Data/ Concomitant Meds | X | X | X | X | X |
| Adverse events | X | X | X | X | X |
| Safety laboratories⁴ (Mandatory study-related) | X | | | | X |
| Study samples⁴ | | | | | |
| Mandatory blood samples (anti-CC10 titer) | X | | | | X |
| Scavenged blood (CC10 tests¹) | | X | X | X | |
| Mandatory TAF (CC10 & inflammatory markers) | X | | | | |
| TAF, if intubated (CC10 & inflammatory markers) | X | X | X | X | X |
| Urine (CC10 tests) | X | X | X | X | X |
| Stool (CC10 tests) | X | X | X | X | X |
| Blood spot for CC10 genotyping³ | X | | | | |

1. CC10 tests: CC10 ELISA, oxidized CC10 biomarker assay
2. Visit 1 CXR, if available. Further head ultrasounds and chest X-rays will be documented, if performed.
3. Blood spot for genotyping may be obtained at the time any sample is being collected for visits 1-5 and may be from scavenged blood.
4. All Visit 1 samples are baseline and should be taken BEFORE study drug is administered.
5. Day 1 = Day of birth

Following the initial dosing and 4 week follow up period is a 12-month follow up period (Period 2) which consists of regular monthly contact by cell phone or visits for assessments (as shown in Table 3). Visit 6 will occur 7 ± 1 days following Visit 5 on day 35 following birth. Visit 6 will also include documentation of vital signs, growth parameters, and physical examination. At the 12 month follow-up visit, a 0.5 mL blood collection will be performed to test for CC10 concentration and antibodies.

TABLE 3: SCHEDULE OF EVALUATIONS (PERIOD 2)

| Evaluation | Visit Number | | | | | | | | | | | | | | | |
|-------------------------------------|----------------|----------------------------|---------------|--------------|---------------|---------------|---------------|---------------|---------------|---------------|---------------|---------------|----------------|----------------|----------------|----------------|
| | 6 day 35 | 7 36 wk ² | 8 40 wk | 9 1 mo | 10 2 mo | 11 3 mo | 12 4 mo | 13 5 mo | 14 6 mo | 15 7 mo | 16 8 mo | 17 9 mo | 18 10 mo | 19 11 mo | 20 12 mo | 21 18 mo |
| TAF, if intubated (CC10 tests) | X | X | X | X | | | | | | | | | | | | |
| O ₂ challenge test | | X | | | | | | | | | | | | | | |
| Hearing screen | | X | | | | | | | | | | | | | | X |
| Bayley Infant ND Assessment | | | | | | | | | | | | | | | | X |
| 6 + 12 month interview & diaries | | | | | | | | | | | X | | | | X | X |
| Physical exam | X | | | | | | | | | | X | | | | X | X |
| Vital signs | X | X | | | | | | | | | X | | | | X | X |
| Growth data | X | X | | | | | | | | | X | | | | X | X |
| Eye exam data ¹ | X | X | | | | | | | | | X | | | | | |
| Discharge interview & summary | | X | | | | | | | | | | | | | | |
| Telephone visit | | | X | X | X | X | X | X | X | X | X | X | X | X | X | |
| Concomitant meds | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | |
| Adverse events | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | |
| Hospital admits + medical visits | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | |
| Respiratory data | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | |
| Study samples | | | | | | | | | | | | | | | | |
| Mandatory blood sample | | | | | | | | | | | | | | | | X |
| (CC10 ELISA-5 ml) | | | | | | | | | | | | | | | | |

1. Eye exams are done and reported only until the retina matures.
2. Visit 7 is at 36 weeks PMA or discharge, whichever comes first.

Visit 7 will occur at 36 weeks CGA ± 3 days. The amount of time between Visit 6 and Visit 7 will vary depending on the gestational age of the infant, and will range from 5 to 7 weeks. Visit 7 (36 weeks CGA ± 3 days) will include Visit 6 parameters as well as a hearing screen, eye examination, baseline parental respiratory questionnaire, and oxygen challenge test. All subsequent visits (both inpatient and outpatient) will occur 30 ± 3 days apart. All follow-up visits will include: review of concomitant medications, eye exam data, adverse events, hospitalizations, medical visits (office, clinic, ER, or hospital), and current respiratory status. Visits 8-13 (40 weeks CGA – 5 months CGA)

will be telephone visits by the study coordinator. Visit 13 (5 months CGA) will include explanation of the 6 month 28-day respiratory symptom and quantitative diaries which will be recorded daily (from 5-6 months CGA) for a 4 week period by filling a hard copy of the 28-day diaries. Visit 14 (6 months CGA \pm 2 weeks) will include Visit 6 parameters, review of the 28-day diaries (presence of persistent coughing, wheezing, or use of respiratory medications for 2 days per week for 3 consecutive weeks out of a 4 week diary period is being used to define CRM), eye examination data, parental respiratory questionnaire (illnesses, medications, medical visits, ER visits, hospital admissions for CRM), and safety laboratories. Visit 15-19 (7 months CGA – 11 months CGA) will be telephone visits. Period 2 will end with Visit 20 (12 months CGA \pm 2 weeks) and will include Visit 6 parameters, review of 28-day diaries, hearing screen, parental respiratory questionnaire, and CC10-related study laboratories (see Table 3). Period 3 follow-ups, beyond 12 months CGA, will include Visit 21 (18 months CGA \pm 2 weeks) which includes Visit 6 parameters, 28-day diaries, parental respiratory questionnaire, and Bayley III Infant Neurodevelopmental Exam. Protocols for standardization of all clinical procedures will be included in the study Manual of Operations (MOO). One month before visit 21 (18 month CGA), study coordinators will send the diaries to the parents/guardians and follow-up with a call to verify that these will be completed and brought in for visit 21 (18 month CGA \pm 2 weeks).

6.5 Monitoring and Management of NEC

NEC is a severe inflammatory response in the GI tract that can occur in preterm infants. The causes of NEC are not well understood. One hypothesis is that increased risk is associated with abnormal colonization of the GI tract by pathogenic bacteria compared to those that normally colonize term infants. NEC may also be related to ischemic bowel injury from peri- or postnatal hypotension or sepsis, absence of maternal antibodies against colonizing organisms, and presence of a patent ductus arteriosus with exposure to indomethacin or ibuprofen. The incidence and severity of NEC will be documented on the CRF and compared between treatment groups (along with other SAE). NEC treatment protocols are standard, but a standardized approach will be outlined in the MOO, which will include NPO with antibiotic coverage for 10 – 14 days in the presence of concerning clinical, laboratory and/or radiographic findings (e.g. pneumatosis, fixed and dilated bowel loops, portal air) or surgery/drainage if the surgeon indicates that this is needed.

6.6 Longer-Term Patient Follow-Up

Infants surviving to discharge will be followed up at each center's Neonatal Follow Up Program until at least 18 months CGA, as specified in section 6.4. Infants will have physical examinations and

formal neurodevelopmental testing, including a Bayley III neurodevelopmental examination at 18 months CGA (considered the gold standard for assessing neurodevelopmental follow-up). At the site's discretion, patient parents/caregivers will be offered a monetary incentive of \$50 for each of three follow-up visits, including bringing the infant to the hospital visits at 6, 12, and 18 months CGA along with the return of 28-day diaries due at each visit.

6.7 Procedure for Collection of Samples

All samples will be labeled only with the type of sample (e.g. serum, TAF, urine, stool), the patient Randomization ID number, and the time and date of collection.

Blood Samples for Electrolytes, CBC and Liver and Renal Function. These samples should be collected according to standard hospital procedure and tested at the hospital laboratory. Initial blood will be obtained from the umbilical cord or placenta, if available. Infant serum or plasma will also be obtained from scavenged samples, if available.

Blood Samples for Anti-CC10 Antibody and CC10 Assay. A single blood sample is required for both tests. Approximately 200 μ L of whole blood will be placed into a serum microtainer, allowed to clot for about ten minutes at room temperature, and then spun in a clinical centrifuge. The serum will be transferred to a sterile microtube and stored at -20°C for analysis by the sponsor. Initial blood will be obtained from the placenta or cord, if available. Drawing of blood required for CC10 tests will be coordinated with collection of blood samples required for routine lab tests, and if possible, from central lines. The total maximum amount of blood to be drawn from each infant for CC10-specific testing for the entire protocol (12 months; 3 samples) is about 3.1 mL.

TAF Samples. TAF samples will be obtained by placing 1 mL of sterile saline into the endotracheal tube, followed by ventilation. A suction catheter is then passed with secretions aspirated into a Leukens trap or other suitable collection device. The catheter is then rinsed with an additional 1 mL of sterile saline. TAF samples will then be spun at 300 x g for 10 minutes at room temperature. The supernatant will then be transferred to a clean labeled tube and frozen immediately at -80°C . Frozen TAF supernatants will be transferred to the Sponsor when sample collection is complete. For samples requiring cell counts, the cell pellet will then be resuspended in 100 μ L of sterile saline and sent to the hospital lab for determination of cell counts and differentials by standard methods. TAF samples will be collected prior to surfactant administration (if medically possible) since suctioning should be avoided after surfactant is given for 1-2 hours. TAF samples will continue to be collected weekly if the infant is still intubated (see tables 2 and 3).

Urine and Fecal Samples. When urine is collected for urinalysis in the hospital laboratory using a bag, excess urine collected should be reserved for CC10 analysis by the Sponsor. (Note: Urine

samples collected using cotton balls are not useful for CC10 measurements and should not be collected for the study.) Each urine sample should be stored at -20°C in a sealed plastic tube that is labeled with the patient Randomization ID, time and date. Fecal material may also be collected from each infant within the first 24-48 hours of life for further analysis of CC10 and oxidized CC10 by the Sponsor. Fecal material will be stored in a sealed plastic tube and labeled with the patient ID, time, and date, and stored at -20°C.

6.8 Analysis of Samples

Blood Samples for Electrolytes, CBC and Liver and Renal Function. Hospital laboratories will carry out these tests. These will include CBC with differential and platelets; serum electrolytes, glucose, BUN, creatinine, ALT, AST, alkaline phosphatase, bilirubin (total and direct), total protein and albumin.

Spots of Whole Blood for CC10 Genotyping. The Sponsor will carry out these tests by extracting genetic material from spotted blood, amplifying the CC10 gene sequences, and sequencing across the four known alleles of the human CC10 gene that are associated with respiratory and autoimmune disorders.

Serum Samples for Anti-CC10 Antibody and CC10 Assay. The Sponsor will test for anti-rhCC10 antibody with standard titrations performed using serial dilutions of serum to bind rhCC10 coated onto 96-well plates. Following this, an anti-human IgG will be used to detect anti-rhCC10 antibodies. To measure rhCC10 in serum, the CC10 ELISA described in the IND CMC section will be used. To measure oxidatively modified/damaged CC10, a new ELISA has been developed.

TAF Samples. The clinical sites will measure cell counts (total cells, neutrophils, etc.). The Sponsor will carry out immunoassays to measure CC10, sIgA, and cytokines (TH2 panel, IL-6, TNF- α , IFN- γ ; Luminex and ELISA). The Sponsor will also use the BCA assay to measure total protein in TAF.

Urine and Fecal Samples. The Sponsor will measure urine and fecal CC10 using the ELISA.

6.9 Concomitant Medications

No other investigational drugs may be administered to patients enrolled in the study. Medications that may be indicated as part of standard care for this group of patients will be administered as needed. Postnatal corticosteroids (other than hydrocortisone utilized for the treatment of early hypotension/adrenal insufficiency) will be avoided, except in cases in which the attending physician determines that the infant's life would be jeopardized without their use. The MOO will include a recommended protocol for postnatal corticosteroid treatment for severe respiratory failure if the clinician feels this therapy is warranted.

Other medications that have a small, but significant impact on the incidence of BPD include Vitamin A and caffeine. Vitamin A is not used in either clinical site and caffeine is administered to all infants within the first 48-72 hours of life (will be seen equally in rhCC10 and placebo treated infants). The impact of all medications will be examined in the final statistical analysis.

7 ADVERSE EVENTS

7.1 Serious, Life-Threatening or Unexpected Adverse Events

Definition of a Serious Adverse Event. Any medical event associated with the use of the drug will be considered a Serious Adverse Event if it results in death, a life-threatening adverse event, prolongation of inpatient hospitalization, a persistent or significant disability or incapacity, or a substantial disruption of the ability to conduct normal life functions. Important medical events that may not result in death, be life-threatening or require prolongation of hospitalization may be considered Serious Adverse Events if, based on appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Clarification of SAE definition. In the context of the definition of an SAE, the phrase “associated with the use of the drug” means that the event is associated with a patient enrolled in the trial and is being reported as a result of the trial. (This is not the same as relatedness of the drug to the event.) An SAE is any adverse event occurring at any dose that; 1) results in death, 2) is life-threatening, 3) results in prolongation of inpatient hospitalization, 4) is likely to lead to a persistent or significant disability or incapacity (including a medically significant event that may require medical or surgical intervention to treat or prevent one of the outcomes, as described in Section 7.3, Section 7.4, and Appendix A), or 5) results in a substantial disruption of the ability to conduct normal life functions. In the context of this trial re-hospitalization for any reason following initial NICU discharge (in follow-up period) is also an SAE. An SAE may be related or unrelated to study medication or study procedures and relatedness is not a consideration in the determination of whether an event is an SAE.

Definition of a Life-Threatening Adverse Event. Any medical event associated with the use of the study drug will be considered a Life-Threatening Adverse Event if it places the patient, in the view of the investigator, at immediate risk of death from the reaction as it occurred.

Definition of an Unexpected Adverse Event. Any Adverse Event associated with the use of the study drug will be considered an Unexpected Adverse Event if, in the view of the investigator, it is not consistent with the typical incidence and severity of the same or similar event among similar patients at the same institution or it is not listed in the investigator brochure.

7.2 Reporting of Serious, Life-Threatening or Unexpected Adverse Events

Serious and Unexpected Adverse Events. Adverse Events that are either serious and/or unexpected must be reported to the Sponsor and CRO as soon as possible after the occurrence. Such events must be reported by the Sponsor to the FDA in writing as soon as possible after the occurrence but in no case more than 7 days (expedited) or 15 days (non-expedited) after the Sponsor's initial receipt of the information.

Unexpected and Fatal or Life-Threatening Adverse Events. Adverse Events that are unexpected and are life-threatening or result in death must be reported to the Sponsor as soon as possible after occurrence. Such events must be reported by the Sponsor to the FDA by facsimile, mail, email, and/or by courier as soon as possible after the occurrence, but in no case more than 7 days after the Sponsor's initial receipt of the information.

All serious, life-threatening, or unexpected adverse events will be reported to the Medical Monitor and to the CRO within 24 hours of the site becoming aware of the event using the CRO's secured e-mail portal.

7.3 Serious Adverse Event Reporting.

Some Adverse Events are of particular importance or concern in the patient population being treated. The purpose of monitoring Serious Adverse Events is to allow the independent DSMB to suspend enrollment in the study if there appears to be a higher incidence of such events among the treated patients than would be expected in a comparable group of premature infants (a difference may be considered clinically significant even though it is not statistically significant due to small patient numbers).

For the purposes of this study, the following will be considered Serious Adverse Events:

- Air leak, including pneumothorax, pulmonary interstitial emphysema (PIE) and, pneumomediastinum significantly impairing gas exchange;
- Pulmonary hemorrhage (requiring blood products and escalating ventilator support);
- Grades III/IV IVH, PVL, seizures;
- Confirmed NEC (\geq Bells stage II, based on attending Neonatologist diagnosis);
- ROP Stage 3 or 4;
- Overwhelming sepsis (early and late – associated with shock);
- Pneumonia
- Death

7.4 Additional Adverse Event Reporting.

The population to be studied in this protocol is at high risk for morbidities associated with prematurity. Events listed below will, for the purposes of this clinical trial, be considered events commonly associated with prematurity. The following morbidities associated with prematurity will be entered on the CRF.

- Air leak syndrome (e.g. pulmonary interstitial emphysema, pneumothorax, pneumomediastinum)
- Anemia of prematurity
- Apnea of prematurity
- Bradycardia
- Periventricular leukomalacia (confirmed by cranial ultrasound)
- Gastrointestinal perforation (confirmed by radiology and surgical pathology to not be associated with necrotizing enterocolitis)
- Hyperbilirubinemia
- Necrotizing enterocolitis (confirmed by radiology; < Bells Stage II)
- Patent ductus arteriosus (confirmed by echocardiography)
- Periventricular or intraventricular hemorrhage (confirmed by cranial ultrasound – grades I, II)
- Sepsis (culture-confirmed from sterile site e.g., blood, CSF, urine)
- Retinopathy of prematurity (Stage II only)

Adverse Events of Nosocomial Infection (specific definitions)

Since rhCC10 is an immunomodulatory protein, special attention will be paid to the AEs associated with nosocomial infection, with a particular emphasis on sepsis, pneumonia, NEC, UTI, and meningitis. A diagnosis of nosocomial infection may be difficult in an intubated neonate and definitions vary. It is recognized that an inflammatory process can arise in the absence of infection. Since uniform reporting is required, the terms sepsis and pneumonia should be reserved for those AEs meeting the criteria defined in Appendix A. In the absence of documented infection, manifestations of a systemic inflammatory response should be listed by underlying etiology or by symptom. Separate summaries of adverse events associated with nosocomial infection will be evaluated on an ongoing basis by the site investigators and the Sponsor and reported to the DSMB, the site IRBs, and FDA as soon as possible after recognition of their importance.

7.5 Criteria for Suspension of the Trial (Stopping Rules).

The DSMB will receive information on the occurrence of Serious Adverse Events on an ongoing basis as patients are enrolled and treated in the study. They will receive the reports and the assignment of infants to groups A, B, or C. If serious adverse events are increased in one group

compared to the other, then the randomization code will be used to determine which of the reported Serious Adverse Events occurred in patients treated with the study drug. If the DSMB determines at any point during the study, using appropriate medical judgment, that there appears to be a greater incidence of Serious Adverse Events related to the study drug among the treated patients than would be expected among similar patients (even if not statistically significant), they will contact the PI and Sponsor and enrollment of patients will be suspended until a determination can be made as to whether the events are related to administration of the study drug.

8 EXPLORATORY ENDPOINTS

Several measures of efficacy in reducing respiratory morbidity in the short and long term will be explored. The trends and effects observed in this study will be used to determine appropriate efficacy outcome variables and the numbers of infants that would be required to be enrolled in a larger Phase 2 or Phase 3 study.

8.1 Primary Endpoint: Long Term Efficacy – 12 months

The primary outcome of the study will be survival without CRM through 12 months CGA as measured by a validated respiratory diary based scoring system (presence of wheezing and/or coughing 2 days per week for 3 consecutive weeks) and pulmonary questionnaires (decrease in respiratory illness requiring medications, unscheduled medical visits and/or ER or hospital admissions) which have been shown to correlate closely with abnormalities on pulmonary function testing. The 12 month CGA endpoint has been shown to be more predictive of respiratory morbidity at two years of life than a diagnosis of BPD at 36 weeks CGA in previous studies of high frequency oscillatory ventilation in preterm infants.

8.2 Secondary Endpoints: Long Term Efficacy – 6 & 18 months

A secondary outcome of the study will be survival without CRM through 6 months CGA as measured by validated respiratory diaries (presence of wheezing and/or coughing 2 days per week for 3 consecutive weeks) and pulmonary questionnaires (decrease in respiratory illness requiring medications and/or hospitalization) which have been shown to correlate closely with abnormalities on pulmonary function testing. Infants will be also be evaluated by physical examinations at 18 months CGA to evaluate respiratory status, growth, and neurological development.

8.3 Secondary Endpoints: Short Term Efficacy

Short term efficacy evaluations will include time of mechanical ventilation, oxygen requirement at 36 weeks CGA, and survival without BPD at 36 weeks CGA (or NICU discharge) as measured by oxygen challenge testing. Oxygen challenge testing involves the withdrawal of supplemental oxygen for a 30 minute period, during which the infant is closely monitored. At the end of the 30' period, oxygenation as

measured by pulse oximetry is recorded and the infant is placed back on supplemental oxygen. The infant's BPD status is then determined by oxygen saturation; a diagnosis of BPD will be made if the infant's oxygen saturation is 90% or less ($\leq 90\%$) at or before the end of the thirty minute period. If the infant's oxygen level remains above 90% for the entire period, then the diagnosis will be "No BPD". Failure to complete the test due to respiratory distress would be scored as severe BPD. The severity of BPD will be assessed using NIH consensus guidelines for infants born at <32 weeks PMA based on oxygen requirements at 28 days post-natal age and at 36 weeks PMA or at NICU discharge (whichever comes first), as described in Jobe and Bancalari. (2001), as follows:

NIH criteria for assessing severity of BPD

| | |
|---|---|
| Gestational age at birth | < 32 weeks PMA |
| Time point of assessment | 36 weeks PMA or DC home, whichever comes first |
| Treatment with oxygen > 28 days plus | |
| Mild BPD | Breathing room air at 36 weeks PMA or DC, whichever comes first |
| Moderate BPD | Need* for <30% oxygen at 36 weeks PMA or DC, whichever comes first |
| Severe BPD | Need* for $\geq 30\%$ oxygen and/or positive pressure (PPV or NCPAP) at 36 weeks PMA or DC, whichever comes first |

Definition of abbreviations: BPD = bronchopulmonary dysplasia; NCPAP = nasal continuous positive airway pressure; PMA = postmenstrual age; PPV = positive-pressure ventilation; DC = discharge.

* Physiologic need for oxygen is determined by oximetry during oxygen withdrawal challenge.

Taken from Jobe AH, Bancalari E. Bronchopulmonary Dysplasia. Am J Resp Crit Care Med 2001;163:1723

8.4 Secondary Endpoints: Safety and Efficacy - Adverse Events

The safety of the study drug will continue to be assessed by comparing the incidence of adverse events and serious adverse events in the treatment and placebo groups to each other and to the historical incidence of the adverse events at each institution. Safety evaluations will include all serious adverse events up to at least 12 months CGA, and routine laboratory monitoring prior to NICU discharge (CBC, electrolytes, liver function studies, urinalysis, head ultrasound). In addition to evaluating the safety of rhCC10, preliminary efficacy of rhCC10 in this patient population may also be indicated by decreases in the numbers of all SAEs and/or specific types of SAEs (ie. IVH, PVL, ROP, sepsis, infection, etc.).

8.5 Statistical Considerations.

Power Analysis: A total of 88 preterm infants will be randomized to placebo, lower dose, or higher dose rhCC10 with an allocation ratio of 2:1:1. The primary analysis will be the comparison of placebo versus both rhCC10 dose groups combined. The prior trial demonstrated that the two doses are likely to yield similar results. Two doses will be used for the purpose of extending the safety profile for each individual dose, as that safety data may facilitate the choice of dose for a future Phase III confirmatory study. For SAEs or AEs with background rates of 5%, 10%, or 15%, the sample size of 22 in either dosing group will provide a probability of observing it of 68%, 90%, and 97%, respectively. The proposed trial is powered for the comparison of the two doses combined versus placebo for the composite endpoint of death or development of CRM. Secondarily, the study will yield effect size estimates for each individual dose versus placebo. Our assumptions regarding the comparison of placebo versus rhCC10 are based on the previous study with 7 placebo, 8 lower dose, and 7 higher dose infants (one infant in each of the rhCC10 treatment groups died). It is important to address the combined endpoint of death or re-admission to the hospital for respiratory problems. In the previous study, one loss-to-follow-up occurred in each of the three experimental groups and one death occurred in each of the rhCC10 groups. At 6 months, 3 of the 6 infants on placebo with follow-up were re-admitted to the hospital for respiratory problems and none of the 11 subjects treated with either rhCC10 dose with follow-up data were re-hospitalized. A realistic and conservative assumption for the 3 lost-to-follow-up babies is that they all either died or had respiratory disease. Then the proportions with disease or death on placebo and rhCC10 are assumed to have been 0.57 and 0.27. If the proportions in the proposed study are similar, with 44 subjects on placebo and 44 subjects in the two dose groups combined, power will be 82% with $\alpha=0.05$. nQuery Advisor version 6 was used.

Data will be summarized for the total cases and by treatment group with respect to: 1) baseline demographic and clinical characteristics and 2) efficacy and safety observations and measurements. Analyses will be conducted on both the intention-to-treat (ITT) and 'per protocol' cases. Between-treatment or between-group comparisons will be examined using chi-square tests (or Fisher's Exact tests when cell frequencies are small) for categorical outcomes and Student t-tests (alternatively, Wilcoxon Rank Sum Test) for scalar measures. Two-sided statistical tests will be conducted and the significance level will be set at 0.05 for each primary test. The efficacy and safety analyses will be conducted on both the ITT and per protocol population. ITT cases will be all randomized subjects who receive the study medication, while per protocol cases will be randomized subjects who complete the study (including all cause deaths) without any major deviations from the protocol procedures. Descriptive statistics will be used to detail the sample characteristics. Between-treatment arm

differences on key baseline demographic and clinical characteristics will be tested. This latter step will be used to identify potential pre-treatment covariates for subsequent secondary analyses. Key baseline variables include race, gender, length, weight, head circumference, SNAPPE-II score, and gestational age. Descriptive statistics for the total exposure to study drug during the treatment period (number of doses), timing of initial study dose, timing of discontinuation in the event of early termination, and rate of study dropout will be provided. Between-treatment differences will be tested using the statistical methods described earlier. Concomitant medications will be summarized by therapeutic/pharmacological class and treatment group. In addition, they will be listed by treatment group, name of drug, dates administered, dose, frequency and indication.

Efficacy evaluation: If CC10 is more efficacious than placebo, the CC10 treatment groups will have a higher rate of survival without BPD at 36 weeks CGA and/or survival without CRM at 12 months CGA (we are exploring which of these factors are more accurate predictors of long term respiratory morbidity). A 2 x 2 chi square test will be conducted to examine treatment differences in this binary endpoint and Kaplan-Meier survival curves will be constructed and any differences between the treatments will be tested using a Cox Proportional Hazards Regression Model. Secondly, a logistic regression will be employed to further detail the main and interaction effects of treatment and centers on the primary outcome. Odds Ratios (OR) with 95% confidence intervals (CI) will be provided. Subjects who die from respiratory causes before 12 months CGA will be considered treatment failures in both the ITT and per protocol analyses, and the last observation carried forward (LOCF) imputation method will be applied for early dropouts. For those subjects without diary data at any time point, respiratory status will be estimated based on available data during the follow-up period, including O₂ challenge test, pulmonary questionnaires, and use of asthma medications.

9 ETHICAL CONSIDERATIONS

9.1 Informed Consent

Written informed consent must be obtained from the infant's parent or legal guardian prior to enrollment of the patient. The patient informed consent will be explained by the attending physician to the parent or guardian who must then sign the form which is included as Appendix B.

9.2 Institutional Review Boards

The study will be reviewed and approved by the Institutional Review Board (IRB) at each of the sites.

Copies of the IRB approval letters will be included as Appendix F.

10 DATA HANDLING, ANALYSIS AND RECORD KEEPING

All records pertaining to this trial will be retained by the Sponsor or participating institutions for FDA inspection. All used and unused drug vials must be accounted for and all used and unused vials must be returned to the Sponsor at the conclusion of the trial.

APPENDIX A: DEFINITIONS OF SPECIFIC ADVERSE EVENTS
CRITERIA FOR ADVERSE EVENTS ASSOCIATED WITH NOSOCOMIAL INFECTION,
AIR LEAKS AND PULMONARY HEMORRHAGE

1. Sepsis

A number of terms confuse the definition of sepsis, including infection, bacteremia, sepsis syndrome, and septic shock. For the purpose of this study, only the term sepsis should be used for AE reporting. Sepsis occurring in the first 3 days after birth (early onset) is considered congenital and should be recorded under past medical history, not as an AE. Sepsis will be defined as the systemic inflammatory response to infection, with criteria adapted from the Centers for Disease Control (CDC) Surveillance of Nosocomial Infection Control Program. All infants with suspected sepsis should have at least 2 sets of blood cultures from 2 separate sites, a urine culture and a cerebral spinal fluid (CSF) culture, with other cultures as determined by the investigator. If a central line is in place, one blood culture should be drawn from the central line (if possible) and one peripherally. A diagnosis of sepsis will require meeting at least one clinical sign or symptom, one invention survey, and one therapy condition.

Definition of nosocomial sepsis

Clinical signs/symptoms Criteria- must meet at least one

Lethargy

Fever ($>38^{\circ}\text{C}$), hypothermia ($<37^{\circ}\text{C}$) or temperature instability

Apnea (increase in frequency and severity from baseline)

Bradycardia (<100 beats/min) or tachycardia (>170 beats/min) (increase frequency and severity from baseline)

Hypotension (mean bp > 10 mm hg below the gestational age with capillary refill time > 5 secs and/or metabolic acidosis on a blood gas)

Oliguria (<1 ml/kg/hour over a 12 hour period)

Infection survey Criterion – must meet

No apparent infection or alternative cause at another site

Therapy Criterion – must meet

Anti-infective drugs given for ≥ 4 days

While all cases meeting the definition of nosocomial sepsis must be recorded as AEs, additional information will be collected on each episode to permit classification of the diagnosis into definite, probable, and no agent identified. Criteria for confirmation of a case of definite sepsis require microbiologic confirmation of an infecting organism. All cases of definite sepsis must meet one of the

criteria defined above. In addition to meeting the definition of nosocomial sepsis, cases of probable sepsis will have one positive blood culture for coagulase negative staphylococcus.

Criteria for the confirmation of a diagnosis of definite sepsis

One blood culture positive for all bacterial, viral, and fungal pathogens other than coagulase negative staphylococcus.

Two positive blood cultures coagulase negative staphylococcus

One positive blood culture and one culture from an otherwise sterile site (CSF, joint, pleural, or peritoneal fluid, bone or deep tissue abscess material) Coagulase negative staphylococcus; urine is excluded as a sterile site unless from a suprapubic tap

Nucleic acid testing, Latex fixation, or PCR assay

Diagnostic single-antibody titer (IgM) or 4-fold increase in paired sera (IgG) for pathogen

2. Pneumonia

Although pneumonia is an important nosocomial infection in the NICU, the diagnosis is often difficult to make due to the inadequacies of current diagnostic methods. For the current trial, pneumonia will be more rigorously defined according to the Centers for Disease Control prevention algorithm. Pneumonia occurring in the first 3 days after birth (early onset) is considered congenital and should be recoded under past medical history, not as an AE. All AEs of pneumonia must meet at least one radiographic, one gas exchange, and 3 clinical or vital signs criteria listed below. **Respiratory manifestations not meeting these criteria should be listed by an alternative etiology (i.e. pneumothorax, aspiration, sepsis, etc.) or by symptom (i.e. apnea, bradycardia).**

Definition of nosocomial pneumonia

Radiographic Criteria – must meet at least one

Persistent new or progressive infiltrate consistent with infection (interstitial, bronchial, or alveolar)

Consolidation

Cavitation

Abscess

Pneumatocele

Gas exchange Criteria – must meet at least one

Oxygen desaturation episodes (increased in frequency and severity from baseline)

Increased oxygen requirement of at least 10 percentage points

Increased ventilation requirement

Clinical/vital signs Criteria – must meet at least 3

Cough

Wheezing, rales or rhonchi

Apnea, tachypnea, nasal flaring with retraction of chest wall, or grunting

New onset of lower respiratory tract secretions, change in character of secretions, or increase in the quantity of secretions or suctioning requirements

Temperature instability

Bradycardia (<100 beats/min) or tachycardia (>170 beats/min)

While all cases meeting the definition of nosocomial pneumonia must be recorded as AEs, additional information will also be collected on each pneumonia episode to permit classification of the diagnosis into probable or definite pneumonia. Criteria for confirmation of a case of definite pneumonia require microbiologic confirmation of an infecting organism. All cases of definite pneumonia must meet one of the criteria defined below.

Criteria for the confirmation of a diagnosis of pneumonia – must meet at least one

Endotracheal aspiration $\geq 10^6$ cfu/ml

Bronchoscopy with BAL $\geq 10^4$ cfu/ml

Positive blood culture for a respiratory tract pathogen

Positive pleural fluid cultures

Isolation of virus or detection of viral antigen in respiratory secretions

Diagnostic single-antibody titer (IgM) or 4-fold increase in paired sera (IgG) for pathogen

Histopathologic evidence of pneumonia

PCR or other genomic identification of respiratory pathogen from lower respiratory tract specimen

3. Air leaks

The group of AEs comprising “air leaks”, and including pneumothorax, pulmonary interstitial emphysema (PIE), and pneumomediastinum, are typically related AEs and often occur in the same patient. Pneumothorax occurs when air collects in the pleural space between the lung and chest wall and can make breathing difficult. PIE occurs in connection with pneumothorax and is detected by radiologic imaging of the lungs. Pneumomediastinum occurs when air leaks into the mediastinum, putting pressure on the heart and lungs.

Pneumothorax

Definitive diagnostic criteria for pneumothorax include increased requirement for respiratory support and chest X-ray showing free air in the chest, collapsed lung and/or displacement of the heart and mediastinum. The most serious cases of pneumothorax require a chest tube to alleviate the pressure on the affected lung.

PIE

PIE is diagnosed radiologically and appears as small round, oval, and/or linear pulmonary lucencies which may be focal or diffuse. Lung volumes are increased and the heart size decreases as intrathoracic pressure increases. If subpleural cysts rupture, PIE potentially may lead to pneumothorax, pneumomediastinum, or even pneumopericardium.

Criteria for the confirmation of a diagnosis of PIE. Confirmation of a diagnosis of PIE is made by a second neonatal radiologist who concurs with the positive diagnosis.

Pneumomediastinum

Pneumomediastinum is confirmed radiologically when a radiolucent outline around the heart and mediastinum is observed in the thoracic cavity.

Air leaks can be life-threatening. For purposes of this study, all air leak AEs will be reported as SAEs and followed closely.

4. Pulmonary Hemorrhage

Pulmonary hemorrhage occurs when blood leaks into the lungs of infants in respiratory distress. It is diagnosed by an increased requirement for respiratory support, bradycardia, drop in blood pressure, and is often associated with patent ductus arteriosis (PDA). Severe pulmonary hemorrhage is treated with increasing end expiratory pressure and supportive blood transfusions. This condition can be life-threatening and will be reported as a SAE.

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Clinical Protocol

Recombinant CC10 Protein

APPENDIX B: INFORMED CONSENT FORMS

Actual Informed Consent Forms for each site are not provided in this protocol Amendment but were provided with IND Serial submission 0035

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Clinical Protocol

Recombinant CC10 Protein

APPENDIX C: NICU DISCHARGE INTERVIEW

(Provided with IND Serial submission 0035)

**APPENDIX D: POST-DISCHARGE VISITS
MONTHLY TELEPHONE VISITS
6, 12, & 18 MONTH INTERVIEWS**
(Provided with IND Serial submission 0035)

Therabron Therapeutics, Inc. (formerly Clarassance, Inc.)

Clinical Protocol

Recombinant CC10 Protein

APPENDIX E: MONTHLY PATIENT SYMPTOM DIARY CARD

(Provided with IND Serial submission 0035)

APPENDIX F: MONTHLY PATIENT QUANTITATIVE DIARY CARD

(Provided with IND Serial submission 0035)