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The Role of Recombinant Human CC10 in the Prevention of Chronic Pulmonary Insufficiency of Prematurity

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Abstract

Background: Preterm neonates can develop chronic pulmonary insufficiency of prematurity (CPIP) later in infancy. Recombinant human CC10 protein (rhCC10) is an anti-inflammatory agent that could potentially prevent CPIP.

Methods: The safety and efficacy of a single intratracheal dose of rhCC10 in reducing CPIP at 12 months corrected gestational age (CGA) was evaluated in a Phase II double-blind, randomized, placebo-controlled, multisite clinical trial. Eighty-eight neonates were randomized: 22 to placebo and 22 to 1.5 mg/kg rhCC10 in the first cohort and 21 to placebo and 23 to 5 mg/kg rhCC10 in the second cohort. Neonates were followed to 12 months CGA.

Results: With CPIP defined as signs/symptoms, medical visits, hospital readmissions, and use of medications for respiratory complications at 12 months CGA, no significant differences were observed between rhCC10 or placebo groups. Only 5% of neonates had no evidence of CPIP at 12 months CGA.

Conclusions: A single dose of rhCC10 was not effective in reducing CPIP at 12 CGA. Since most neonates had evidence of CPIP using these exploratory endpoints, it is essential to develop

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more robust outcome measures for clinical trials of respiratory medications in high risk premature neonates.

INTRODUCTION

Each year in the U.S., about 12% of births (~500,000 neonates) are born prematurely and there is an urgent, unmet medical need for therapeutic interventions to improve long term clinical outcomes in this population. Bronchopulmonary dysplasia (BPD) is a form of chronic lung disease that develops in preterm neonates who initially required supplemental oxygen and positive pressure ventilatory support (1). Although the pathogenesis of BPD is complex, damage from oxidation and associated lung inflammation plays a prominent role. While anti-inflammatory agents such as dexamethasone and hydrocortisone may decrease the risk of BPD in preterm neonates, unacceptable side-effects (e.g. death, cerebral palsy, intestinal perforation) have precluded the routine use of these agents (2,3). BPD has traditionally been defined using short-term endpoints such as the use of supplemental O_2 at 36 weeks post-menstrual age (PMA). However, ~50% of neonates receiving O_2 at 36 weeks PMA actually develop longer term respiratory morbidity which has recently been described as Chronic Pulmonary Insufficiency of Prematurity (CPIP – breathing difficulties, repeated pulmonary infections). In addition, 30% of premature neonates not receiving O_2 at 36 weeks PMA may still develop CPIP (4,5).

The Club cell 10 kilodalton protein (CC10) is an anti-inflammatory, immunomodulatory protein highly expressed by the airway epithelium in all mammals. Endogenous CC10 concentration in the fetal lung rapidly increases after 28 weeks gestation and is a biomarker of fetal lung development, similar to antioxidant enzymes and pulmonary surfactant (6). Most importantly, preterm infants who die or develop severe lung injury have been shown to be deficient in native CC10 (less expression, increased oxidation) (7).

Recombinant human CC10 protein (rhCC10) is a novel therapeutic agent developed for the prevention or treatment of respiratory diseases associated with marked inflammation. rhCC10 administration has been shown to significantly improve lung structure and function in animal models of lung injury by: 1) reducing lung inflammation; 2) upregulating important growth factors (e.g. vascular endothelial derived growth factor, surfactant proteins); and 3) reducing injury from hyperoxia, endotoxin, and infection (8,9).

In a small Phase 1 trial of rhCC10 in premature neonates, a single intratracheal (IT) dose administered within 24 hours of birth following surfactant administration significantly reduced inflammatory indices (e.g. total cell counts, neutrophils, total protein, IL-6) in tracheal aspirates (10). Of the 22 infants enrolled, there were two deaths in the rhCC10 treatment groups and none in the placebo group. In addition, follow-up at 6 months corrected gestational age (CGA) indicated that treatment with rhCC10 was associated with a reduced number of respiratory associated hospitalizations, treatment with bronchodilators, and total number of respiratory infections (Table 1). The present study is a randomized, double-blinded, placebo-controlled, dose escalation Phase 2 trial that enrolled 88 preterm neonates at 24–29 weeks gestation at birth. Neonates were then followed to one year CGA to

evaluate safety and short and long term efficacy using several novel exploratory endpoints to assess the presence of CPIP.

METHODS

Study medication:

The rhCC10 study medication was supplied by Therabron Therapeutics, Inc. (Rockville, MD) in a 5.5 mg/ml formulation that was diluted to 1.5 or 5 mg/kg (volume was constant at 2 ml/kg). The placebo was normal saline. The pharmacist received a computer generated, randomized treatment assignment at enrollment. The rhCC10 study drug was a clear colorless liquid indistinguishable from placebo. All other hospital personnel were blinded to the treatment received.

Dose selection:

The Phase 1 clinical trial evaluated doses of 1.5 mg/kg and then 5.0 mg/kg (in 2 ml/kg) in premature neonates and was based on safety and efficacy analyses in several animal models (10, 11). Similar escalating dosage approaches were used in the present trial, with an initial low-dose cohort enrolling 50% of the neonates followed by a second high-dose cohort that enrolled the remainder of the sample.

Drug administration:

The single dose of study drug was administered intratracheally within the first 24 hours of life and within 4 hours of the first dose of exogenous surfactant (Curosurf™). Doses were calculated based on the neonate's birthweight. The drug was administered in an identical fashion to surfactant administration.

Study Design:

The study used a multicenter, double-blind, placebo-controlled, randomized, dose-escalation design. In the first cohort (n=44), neonates were randomized to either placebo or 1.5 mg/kg rhCC10. Following a safety assessment by the Data Safety Monitoring Board (DSMB), the second cohort (n=44) was randomized to either placebo or 5 mg/kg rhCC10.

Inclusion criteria:

1) ≤24 hours of age, 2) 24 0/7 – 29 0/7 weeks gestational age at birth based on best estimate using obstetrical sonography (first or second trimester), solid dating criteria, or Ballard examination, 3) birth weight 600–1200 g, 4) 5 minute Apgar score >5, 5) diagnosis of respiratory distress syndrome (clinical, radiographic criteria), 6) intubated and receiving positive pressure mechanical ventilation, 7) growth parameters at birth appropriate for gestational age; 8) received at least one dose of surfactant, and 9) parent or guardian has signed informed consent.

Exclusion criteria:

1) 5 minute Apgar score of ≤5, 2) major congenital anomaly (chromosomal, renal, cardiac, neurologic, or pulmonary malformations), 3) congenital infection, 4) use of postnatal

corticosteroids before enrollment, 5) mother and/or neonate enrolled in another clinical trial of an investigational drug, 6) requirement for a major surgical procedure within the first 48 h of life, 7) use of inhaled nitric oxide, 8) mother known to be seropositive for HIV, and 9) parent or guardian unable or unwilling to complete study procedures after hospital discharge.

Enrollment/Randomization:

In each cohort, subjects were randomized to either placebo or rhCC10. Treatment was stratified by gestational age (24 0/7 – 27 0/7; 27 1/7 – 29 0/7 weeks) and clinical center. Multiple births were randomized separately in order of birth. The protocol was approved by the Institutional Review Board (IRB) at each participating institution.

Post-discharge visits:

Following discharge, mothers for each neonate were contacted monthly to obtain real-time information and visits were scheduled at 6 and 12 months CGA for clinical evaluation. Parents filled out comprehensive diaries daily for 4 consecutive weeks from 5–6 months and 11–12 months CGA (5). Diaries documented wheezing, coughing, and the use of respiratory medications (steroids, bronchodilators, leukotriene inhibitors) secondary to significant respiratory illness. Positive findings were reported as coughing, wheezing, or respiratory medication use at least 2 days per week for at least 3 consecutive weeks over 4 consecutive weeks. Pulmonary questionnaires previously developed for the SUPPORT trial were also used (12).

Interim Safety Evaluations:

The DSMB performed safety assessments, evaluating all Adverse Events (AE) and Serious Adverse Events (SAE) when 25%, 50%, and 75% of infants were enrolled. A preplanned pause in enrollment occurred at the end of the first cohort. An unplanned pause in enrollment occurred at the request of the DSMB when 75% of infants were enrolled for the purpose of conducting a comprehensive review of all deaths in the study. Upon completion of the review, enrollment was continued and enrollment was completed.

Clinical Trial Sites:

The first low-dose cohort of 44 neonates was enrolled at two centers in Boston, MA (Tufts Medical Center, Brigham and Women’s Hospital). Due to slow enrollment, multiple US sites were contacted during and invited to participate in the second cohort of the study. One site (BayState Medical Center, Springfield, MA) did not have any ongoing studies that would compete with this trial and agreed to participate. All other US sites declined. In addition, orphan drug designation was awarded in Europe, so three new European sites with experience in neonatal clinical trials were added for the second high-dose cohort of 44 neonates, including Ginekologiczno-Położniczy Szpital Kliniczny UM (Poznan, Poland), Instytut Centrum Zdrowia Matki Polski (Lodz, Poland), and Samodzielny Publiczny Zakład Opieki Zdrowotnej Szpital Uniwersytecki w Krakowie (Krakow, Poland).

Primary Outcome Measure:

The primary combined endpoint was survival without evidence of CPIP at 12 months CGA. CPIP was defined a priori as the presence of one or more parent-reported outcomes at 12 months CGA including: 1) evidence of respiratory symptoms (e.g. coughing and wheezing) or use of respiratory medications by parental diaries or pulmonary questionnaires (CPIP-SS), 2) one or more re-hospitalizations for respiratory causes (CPIP-RH), 3) administration of respiratory medications (including oxygen) (CPIP-RM), and 4) at least one non-routine medical visit for respiratory causes (CPIP-DV). Neonatal outcomes were graded as being positive for 1, 2, 3, or 4 of these components. Other exploratory efficacy endpoints of interest were: a) alive without evidence of CPIP at 6 months CGA and b) evidence of CPIP in survivors at 6 and 12 months CGA.

Safety Endpoints:

Safety evaluations included all SAEs before and after NICU discharge and routine laboratory monitoring (CBC, electrolytes, liver function studies, urinalysis). Less serious adverse events (AEs) were also monitored and recorded prior to NICU discharge.

Anti-Drug Antibody (ADA) Testing:

Western blots were performed of serum samples collected at baseline (pre-dosing), 28 or 35 days of life, and/or at 12 months CGA. Briefly, rhCC10 was run on SDS-PAGE (55 mcg/well), reduced and non-reduced, and incubated in 10 μL serum diluted 1:1000 in 5% Blotting Grade Blocker and incubated overnight at 4°C. The samples were washed, then incubated with rabbit anti-human IgG antibody alkaline phosphatase conjugate diluted 1:20,000 in 0.1% Blotting Grade Blocker and incubated 1hr at room temperature. The blot was then washed and developed. Each blot of 4 lanes had a pre-stained size standard, reduced and non-reduced rhCC10, and purified E. coli malate dehydrogenase was used as a positive control. A total of 43/88 subjects had all 3 sequential samples available for analysis.

Growth and Neurologic Outcomes:

Serial physical and neurological examinations at 6 and 12 months CGA were performed. Growth measurements (weight, length, head circumference) were used to examine the relationship between CPIP, treatment, and growth.

Statistical Analysis:

Sample size calculation: The prior trial demonstrated that the two doses were likely to yield similar results and were combined to form the basis for the short and longer-term outcomes in the present trial (10). If the proportions of deaths or neonates developing CPIP in the present study were similar (57% in the placebo group and 27% in the treated group), 44 subjects on placebo and 44 subjects in the two combined rhCC10 dose groups would provide 82% power to detect this difference using a chi-square test with α=0.05. The two different doses were also used for the purpose of extending the safety profile for each individual dose. For SAEs or AEs with background rates of 5%, 10%, or 15%, the sample size of 22 in either dosing group provided a probability of observing at least one instance of 68%, 90%, and 97%, respectively.

Analysis Plan: The primary analysis was the comparison of placebo versus each rhCC10 dose group for the composite endpoint of survival without evidence of CPIP at 12 months CGA. Analyses of treatment effect were performed according to the intention-to-treat principle. Within each cohort, the proportion of neonates in each treatment arm who met criteria for the various definitions of CPIP were compared using chi-square tests. If data were missing for any given component, the worst-case was imputed. The proportion of neonates in each treatment arm who experienced AEs and SAEs was compared using Fisher's exact tests. Differences in growth parameters were compared with t-tests. All statistical tests were 2-sided with a significance level of $\alpha = 0.05$. Analyses were performed using SAS software, version 9.4_M3 (SAS Institute, Cary, NC).

RESULTS

A total of 88 preterm infants were randomized in the trial: 44 in the low-dose cohort (22 placebo and 22 rhCC10) and 44 in the high-dose cohort (21 placebo and 23 rhCC10) (Figure). Table 2 shows trial demographics and baseline characteristics by treatment group. Approximately half of the neonates (n=23) in the second cohort were enrolled at Polish sites and there were significant demographic differences between cohorts with a higher proportion of Caucasian neonates in the second cohort (75% vs 48%, p=0.009). Gender, gestational age at birth, birthweight, and 5' APGAR scores were all comparable between cohorts.

Growth:

There were no significant differences between groups with respect to the mean weight, length, or head circumference of neonates at birth, 6, and 12 months CGA.

Mortality and safety:

The overall survival rate in the study was 90% (79/88 infants). Two of the deaths were in the 1.5 mg/kg rhCC10 group, 5 were in the 5 mg/kg rhCC10 group, and 2 were in the placebo group (both in the second cohort). There were no significant differences in mortality between groups. None of the deaths were thought to be related to study medication. The causes of death were varied and typical of this population.

There were 912 AEs and 198 SAEs in the 88 neonates enrolled in the study. Table 3 shows that there were no significant differences in the number of AEs and SAEs between placebo and rhCC10 treatment groups in each cohort. One hundred forty-five SAEs occurred before NICU discharge and 53 after discharge. Of these 53 post-discharge SAEs, 51 were respiratory infections. There were also no differences between the low and high dose rhCC10 groups with respect to AEs and SAEs. Serial serum samples for ADA testing demonstrated no evidence of anti-drug antibodies in any sample.

Efficacy:

Using our a priori definition of CPIP, only 5% of neonates in the first cohort (a single neonate in each arm) and 14% of neonates in the second cohort had none of the CPIP components at 12 months CGA (Table 4). Overall, administration of a single intratracheal

dose of rhCC10 did not appear to significantly improve respiratory outcome in either treatment group when compared to placebo. In addition, results did not change when the two treatment groups were combined and compared to the two placebo groups. Sub-group analyses (not part of the a priori definition) demonstrated that the proportion of neonates with 3 or fewer components of CPIP at 12 months CGA was significantly higher in the placebo group than the low dose rhCC10 group. These analyses also indicated that a greater proportion of neonates in the low dose rhCC10 met criteria for all 4 CPIP components compared to those who received placebo. This difference between arms was not observed in the high dose cohort.

To understand the relative contributions of the four types of exploratory CPIP components, the number of neonates scoring positive for each individual component was evaluated. The distribution at 12 months CGA is shown in Table 5. The number of neonates without any non-routine (unscheduled) respiratory medical visits and respiratory re-hospitalizations was significantly higher in the placebo than the low dose rhCC10 regardless of imputation for death and missing data. However, no significant differences were seen in any CPIP component in the second cohort when placebo was compared to high dose rhCC10.

The most widely used definition of BPD is the use of oxygen at 36 weeks PMA which was an important secondary outcome. There were no significant differences between treatment groups in either cohort, or between cohorts, in the number or percent of neonates that were alive without BPD at 36 weeks PMA, or in the number of survivors that were on oxygen at 36 weeks PMA. In addition, neonates who were alive without BPD at 36 weeks PMA had fewer CPIP components at 12 months CGA (Table 6).

Environmental and genetic risk factors for CPIP:

Table 7 shows the frequencies of neonates by treatment groups (placebo vs rhCC10) with various risk factors for CPIP. Each neonate exposed to cigarette smoke experienced one or more components of CPIP.

DISCUSSION:

The present study was a Phase II dose escalation clinical trial to evaluate the efficacy of a single intratracheal dose of rhCC10 in preventing development of CPIP in significantly premature neonates. rhCC10 is an anti-inflammatory, immunomodulatory factor secreted primarily by the airway epithelium and is known to inhibit phospholipase A2 enzymes which can play a role in surfactant degradation and inflammation (14). A Phase 1 study of a single dose of rhCC10 or placebo in 22 preterm infants appeared to be safe and reduced lung biomarkers of inflammation without a reduction in BPD endpoints (10). In addition, subsequent analysis at 6 months CGA revealed potential long-term pulmonary benefits as described in Results. Therefore, the present trial was designed in a similar fashion using a single dose treatment strategy.

The present study was designed to evaluate the impact of rhCC10 on the continuum of respiratory sequelae of prematurity from birth to 12 months CGA. It was a major priority of the study to develop viable and clinically meaningful CPIP endpoints that would be

important to health care providers, families, and regulators. The power analysis for the 12 month CGA assessments was based on the 6 months CGA outcome data in the Phase 1 trial in 22 preterm neonates that met similar inclusion/exclusion criteria as the present study. Data were collected through 12 months CGA in order to compare BPD outcomes at 36 week PMA with longer-term outcomes. This is the first interventional drug study to utilize novel, prospective, exploratory long-term endpoints focused on CPIP as the primary outcome.

In the Phase 1 study, there were two deaths in 22 infants, one in the low dose rhCC10 group and one in the high dose rhCC10 group. In the present Phase 2 study, there were two deaths in the low dose rhCC10 group, five deaths in the high dose rhCC10 group, and two deaths in the placebo group. The mortality rate in rhCC10-treated groups was not significantly different compared to placebo groups. Although all of the deaths were typical of this population and none were considered related to rhCC10 treatment, the Data Safety Monitoring Committee performed a comprehensive review at 75% enrollment before allowing the study to be completed. It is likely that regional differences in survival between the US (92%) and Poland (83%) where neonates were only enrolled in the second cohort could explain some of the increased mortality (15). No discernible pattern of toxicity emerged from analysis of AEs and SAEs, suggesting that rhCC10 appeared to be safe.

There were no significant differences between groups for individual or combinations CPIP components. It is important to note that there were three times as many mothers that smoked during pregnancy and/or postnatally in both rhCC10-treated groups compared to controls. Maternal smoking is a known risk factor for impaired lung function, wheezing, and asthma in children (16). Recent research has also suggested an interaction of in utero and early-life smoke exposure with up-regulation of asthma susceptibility genes, which may have negatively impacted CPIP outcomes in the rhCC10 groups (17). It will be important to develop appropriate methodologies to consider environmental, life-style, genetic predisposition, and other factors that impact long term respiratory health (e.g. asthma) in future studies.

Another goal of this study was to explore novel outcomes to be used in future interventional trials, since a diagnosis of BPD has poor positive predictive value for long-term respiratory outcome (18, 19). Previous studies have developed respiratory symptom scores which incorporate the frequency and severity of coughing and wheezing and respiratory medication use based on parental diaries and pulmonary questionnaires, as potential measures of long term CPIP outcomes (5,12,20). Other investigators have analyzed large cohorts of preterm neonates (retrospective and prospective) in order to develop short (e.g. 40 weeks PMA) and longer term (1–2 years CGA) pulmonary outcome measures that can more accurately predict the development of CPIP (21,22). It is clear that a 1 year CGA respiratory outcome is more advantageous than shorter term outcomes. However, validation of data collection tools, comprehensive follow-up, and the ability to control for environmental factors following discharge are definitely needed. It may be necessary to prioritize individual components and provide a “weight” for each one (e.g. a visit to the pediatrician is less burdensome to families than an intensive care unit admission). Further studies in which both 36 week PMA and longer term data are collected and correlated are necessary in order to develop optimal clinical endpoints for assessing outcomes in interventional clinical trials.

The overall conclusion is following a single dose of rhCC10 into the lung, we were not able to significantly improve our clinical endpoints at 12 months CGA. It is possible that our exploratory pulmonary outcomes did not have adequate sensitivity to detect benefit or harm. It is also possible that 12 months may be too early to prove or disprove benefit. The binary outcomes for our CPIP domains may have lost sensitivity that may reside in data from continuous variables. It is also possible that a single dose of rhCC10 was inadequate to impact longer-term outcomes and that multiple dose treatment strategies may be needed. This was demonstrated with studies in premature neonates of recombinant human superoxide dismutase where a single dose was noted to have no impact, but multiple doses were found to significantly improve longer-term respiratory outcomes (23). It is clear that before future therapeutic intervention trials can be conducted in this high risk population, more robust outcome measures are urgently needed.

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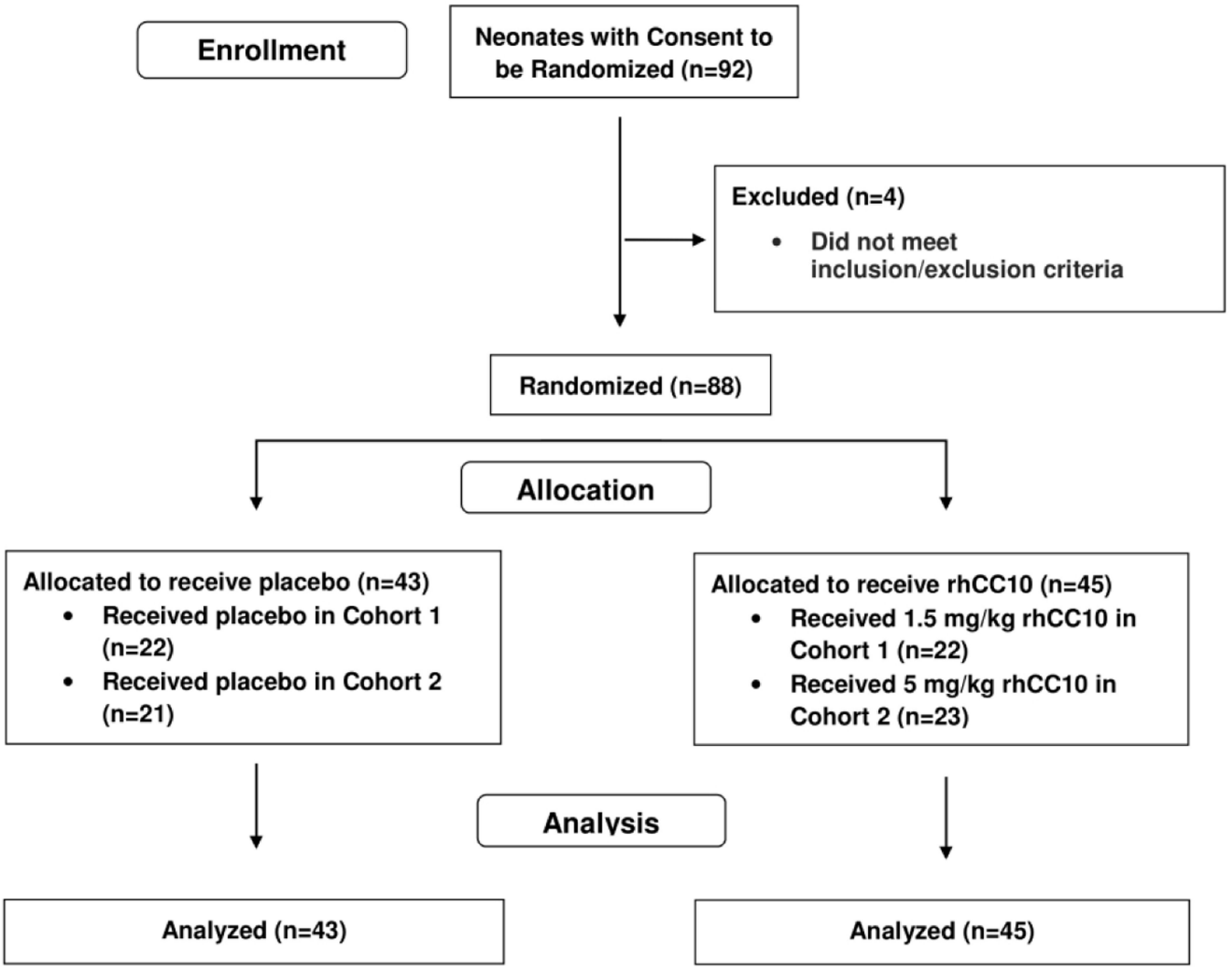

Figure Legend:
CONSORT Flow Diagram

Table 1:

Phase 1 Clinical Trial Outcomes at 6 months CGA

	Placebo	1.5 mg/kg	5 mg/kg
# infants with respiratory re-hospitalizations at 6 months CGA	3/6	0/6	0/5
# infants using bronchodilators at 6 months CGA	5/6	0/6	0/5
# deaths	0/7	1/8	1/7

Denominators are numbers of infants with available data. CGA – corrected gestational age

Levine CR, Gewolb I, Allen K, Welsh RW, Melby JM, Pollack S, Shaffer T, Pilon A, Davis JM. Safety, pharmacokinetics, and anti-inflammatory effects of intratracheal recombinant human clara cell protein in premature infants with respiratory distress syndrome. Pediatr Res 2005;58:15–21.

Table 2:

Trial Demographics by Treatment Group

Demographic	Placebo (N=22)	1.5 mg/kg rhCC10 (N=22)	Placebo (N=21)	5 mg/kg rhCC10 (N=23)
Region – N (%) US Poland	 22 (100) N/A	 22 (100) N/A	 10 (48) 11 (52)	 11 (48) 12 (52)
White - N (%)	9 (41)	12 (55)	15 (71)	18 (78)
Hispanic ethnicity – N (%)	5 (23)	7 (32)	5 (24)	5 (22)
Female – N (%)	12 (55)	8 (36)	8 (38)	12 (52)
Mean gestational age at birth (SD) – weeks	26.1 (1.3)	26.5 (1.1)	27.0 (1.3)	26.6 (1.2)
Mean birth weight (SD) – grams	877.4 (170.9)	859.3 (140.9)	885.5 (173.9)	867.2 (187.2)
Median 5 minute APGAR score (IQR)	8 (7, 8)	7 (6, 8)	7 (7, 8)	7 (6, 8)

SD – Standard Deviation; IQR – Interquartile Range; N/A – not applicable

Table 3:

Major SAEs by Treatment Group (Birth through 12 months CGA)

AE Term	Placebo	1.5 mg/kg rhCC10	Placebo	5 mg/kg rhCC10
All SAEs	39	36	56	62
ROP stage 3	5	1	3	4
IVH grade 3–4	0	1	4	4
PVL	0	0	3	0
PDA	0	1	2	3
Sepsis	1	3	4	6
NEC stage 2–3	3	1	2	2
Intestinal perforation	2	0	1	0
Respiratory SAEs				
Respiratory infections	12	4	19	17
Multiple respiratory infections	2	1	5	4
Respiratory distress	1	3	0	4
Respiratory acidosis	0	0	2	0
Pulmonary hemorrhage	1	1	2	2
Pulmonary hypertension	0	1	1	0
Pulmonary Interstitial Emphysema	1	1	0	1
Pneumothorax	3	1	0	0
Apnea	4	5	2	0

SAEs – serious adverse events; ROP – retinopathy of prematurity; IVH – intraventricular hemorrhage; PVL – periventricular leukomalacia; PDA – patent ductus arteriosus; NEC – necrotizing enterocolitis

Table 4:

Number of CPIP Components at 12 Months CGA

Cohort	Number of Components	N (%) infants surviving without CPIP at 12 months CGA			N (%) infants without CPIP in survivors at 12 months CGA		
		Placebo	rhCC10	P-value	Placebo	rhCC10	P-value
Cohort 1	N	22	22		22	20	
	None	1 (5)	1 (5)	>0.9	1 (5)	1 (5)	>0.9
	≤1 component	5 (23)	3 (14)	0.4	5 (23)	3 (15)	0.5
	≤2 components	13 (59)	7 (32)	0.07	13 (59)	7 (35)	0.1
	≤3 components	21 (95)	13 (59)	0.004	21 (95)	13 (65)	0.01
Cohort 2	N	21	23		19	18	
	None	3 (14)	3 (13)	0.9	3 (16)	3 (17)	0.9
	≤1 component	5 (24)	6 (26)	0.9	5 (24)	6 (33)	0.6
	≤2 components	8 (38)	7 (30)	0.6	8 (42)	7 (39)	0.8
	≤3 components	13 (62)	10 (43)	0.2	13 (68)	10 (56)	0.4

a: Imputed worst-case scenario for missing data.

b: No imputation for missing data; denominators reflect numbers of patients for whom data were collected at this time point

CPIP – chronic pulmonary insufficiency of the prematurity

Table 5:

Individual CPIP components at 12 months CG A

Cohort	Type of Component	N (%) survival without CPIP at 12 months CGA[a]			N (%) without CPIP in survivors at 12 months CGA[a]		
		Placebo	rhCC10	P-value	Placebo	rhCC10	P-value
Cohort 1	N	22	22		22	20	
	None	1 (5)	1 (5)	>0.9	1 (5)	1 (5)	>0.9
	No CPIP-DV (Medical/ER visits)	8 (36)	2/21 (10)	0.04	8 (36)	2/19 (11)	0.055
	No CPIP-RH (Respiratory hospitalizations)	20 (91)	12 (55)	0.007	20 (91)	12 (60)	0.02
	No CPIP-SS (Respiratory Symptoms)	2/22 (9)	3/21 (14)	0.6	2 (9)	3/19 (16)	0.5
	No CPIP-RM (Respiratory Medications)	10 (45)	7/21 (33)	0.4	10 (45)	7/19 (37)	0.6
Cohort 2	N	21	23		19	18	
	None	3 (14)	3 (13)	0.9	3 (16)	3 (17)	0.9
	No CPIP-DV (Medical/ER visits)	6 (29)	6/22 (27)	0.9	6 (32)	6/17 (35)	0.8
	No CPIP-RH						
	(Respiratory re-hospitalizations)	11 (52)	10/22 (45)	0.6	11 (58)	10/17 (59)	>0.9
	No CPIP-SS (Respiratory Symptoms)	6 (29)	5/22 (23)	0.7	6 (32)	5/17 (29)	0.9
	No CPIP-RM (Respiratory Medications)	6 (29)	5/22 (23)	0.7	6 (32)	5/17 (29)	0.9

[a]: No imputation for missing data; denominators reflect actual numbers of patients for whom data were collected at this time point.

CPIP – chronic pulmonary insufficiency of the prematurity; DV – unscheduled doctor and emergency room visits, RH – respiratory hospitalizations, SS – signs/symptoms respiratory disease, RM – respiratory medications including oxygen

Table 6:

Number of CPIP Components at 12 Months CGA by BPD at 36 weeks

Cohort	Number of Components	Alive without BPD at 36 weeks PMA*	
		Yes	No
Cohort 1	N	24	20
	None	1 (4)	1 (5)
	≤1 component	6 (25)	2 (10)
	≤2 components	16 (67)	4 (20)
	≤3 components	22 (92)	2 (60)
Cohort 2	N	26	18
	None	6 (23)	0
	≤1 component	9 (35)	2 (11)
	≤2 components	11 (42)	4 (22)
	≤3 components	15 (58)	8 (44)

Table 7:

CPIP Risk Factors*

	Cohort 1		Cohort 2	
N (%)	**Placebo (n=22)**	**rhCC10 (n=20)**	**Placebo (n=19)**	**rhCC10 (n=18)**
Parental allergy and asthma	7/21 (33)	/20 (60)	5/19 (26)	4/18 (22)
Smoking during pregnancy	0/21 (0)	4/19 (21)	2/18 (11)	3/18 (17)
Received Synagis	18/22 (82)	19/20 (95)	16/19 (84)	17/18 (94)
Pets in home	7/21 (33)	10/20 (50)	8/19 (42)	5/18 (28)
Smoking in the home	1/21 (5)	0/19 (0)	0/19 (0)	2/18 (11)

*Among infants who survived to 12 months CGA. Denominators vary due to missing data.