Randomized Controlled Trial of Budesonide + Surfactant versus Surfactant Alone in Extremely Preterm Infants ("The Budesonide in Babies (BiB) Trial")

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SECTION 1. ABSTRACT

Study Hypothesis/Question
Early intratracheal administration of a combination of budesonide with surfactant (Intervention), as compared to surfactant alone (Active control) will reduce the incidence of physiologic bronchopulmonary dysplasia (BPD) or death by 36 weeks' post-menstrual age in extremely preterm infants.

Study Design Type
Randomized, masked, active-controlled multicenter clinical trial with 1:1 allocation to two treatment arms.

Eligibility Criteria
Inclusion criteria: Liveborn infants 22 $^{0}/_{7}$ – 28 $^{6}/_{7}$ weeks gestation OR 401 – 1000 grams (inclusive) birth weight with clinical decision to give surfactant. Infants must be enrolled into the trial early so that the first dose of study drug can be administered ≤ 50h postnatal age, and may be consented antenatally or postnatally.

Exclusion criteria: Use of surfactant before enrollment (first dose of surfactant must be study drug); infant received systemic steroids prior to enrollment; use of indomethacin, either received by the mother within 24 hours prior to delivery, received by the infant prior to enrollment, or intent to administer to the infant for IVH prophylaxis or PDA management from enrollment up to 7 days of final dose of study drug; known congenital infection; serious chromosomal abnormalities or major malformations; a permanent neuromuscular condition that affects respiration; terminal illness (heart rate < 100 beats per minute, unresponsiveness to resuscitation) or unlikely to survive; or decision to redirect or limit support; enrollment in a conflicting clinical trial.

Study Intervention/Methods
After informed consent and assessment of eligibility, infants will be randomized 1:1 to either the budesonide + surfactant arm or the surfactant alone arm. Randomization will be stratified by study site (NICU) and by gestational age (< 26 weeks; ≥ 26 weeks). The research pharmacy will receive a computer-generated code number that will be linked to each enrolled infant upon randomization. The corresponding budesonide + surfactant or surfactant alone will be administered by an unmasked respiratory therapist or other qualified person in participating neonatal ICUs, while other caregivers will remain masked to treatment group allocation. Multiple gestations (if more than one is eligible) will be randomized independently. The intervention arm will receive surfactant (poractant alfa; Curosurf) 2.5 ml/kg mixed with 0.25 mg/kg budesonide (Pulmicort nebulizing suspension or equivalent generic) while the active control arm will receive Curosurf 2.5 ml/kg for the first dose. A maximum of two doses of study drug can be administered, with specific criteria for the second dose at ≤ 50h age.

Primary Outcome
Physiologic BPD or death by 36 weeks post-menstrual age (PMA)

Secondary Outcomes
Death by 36w PMA; Physiologic BPD at 36w PMA; BPD severity by the Jensen et al. (2019) definition at 36w PMA (No BPD/Grade 1/Grade 2/Grade 3); Grade 3 BPD at 36w PMA; use of postnatal steroids for chronic lung disease by 36w PMA; severe neurodevelopmental impairment (NDI) assessed at 22-26 months corrected age; death by 22-26 months corrected age assessment; severe NDI/death by 22-26 months corrected age.

Exploratory Outcomes
BPD severity (None/Mild/Moderate/Severe) at 36w PMA by the NICHD definition (Jobe and Bancalari 2001); number of days on invasive mechanical ventilation by postnatal day 28; number of days on invasive mechanical ventilation by 36w PMA; intubation after the treatment window and by postnatal day 28; intubation after the treatment window and by 36w PMA; administration of repeat surfactant doses after the treatment window; respiratory outcomes (recurrent wheezing and chronic coughing) by 22-26 months corrected age.

Safety Outcomes
Within the first week following last study drug administration (hypertension, hyperglycemia, prolonged hypoxemia with bradycardia, endotracheal tube blockage, hypotension, pulmonary air leak, sepsis, intracranial hemorrhage); within 30 days following last study drug administration (spontaneous intestinal perforation, periventricular leukomalacia); impairment of growth parameters assessed at 36w PMA (weight, length, head circumference)

SECTION 2. CONFLICT OF INTEREST DISCLOSURES

Per Title 42, Code of Federal Regulations, Part 50, Subpart F (50.604 Responsibilities of Institutions regarding Investigator financial conflicts of interest), as amended, institutions and all subrecipients are required to notify the grants officer of any financial conflicts of interest (FCOI) prior to expenditure of any funds and within 60 days of any subsequently identified FCOI.

Financial Conflicts of Interest of the Institutions and Investigators
No conflicts of interest exist with commercial entities. Collaborators Drs. Roberta and Phil Ballard and Dr. Cindy McEvoy are funded by a grant from the Thrasher foundation to evaluate the optimal dosing of budesonide with surfactant.

Plan for Managing Identified FCOIs
Identified FCOIs will be managed as per usual NRN protocol.

SECTION 3. STATEMENT OF PROBLEM

3.1. PRIMARY HYPOTHESIS

The primary hypothesis is that early intratracheal administration of a combination of budesonide with surfactant (Intervention), as compared to surfactant alone (Control) will reduce the incidence of physiologic bronchopulmonary dysplasia (BPD) or death by 36 weeks' (w) post-menstrual age (PMA) in extremely preterm infants.

3.2. SECONDARY QUESTIONS

Secondary questions are if early intratracheal administration of a combination of budesonide with surfactant, as compared to surfactant alone, will reduce the incidence of:

- Death by 36w PMA
- Physiologic BPD at 36w PMA
- Higher severity BPD as defined by Jensen et al. (2019) at 36w PMA according to treatment with the following support:
    - No BPD, room air;
    - Grade 1, nasal cannula at flow rates ≤2 L/min;
    - Grade 2, nasal cannula at flow rates >2 L/min or noninvasive positive airway pressure;
    - Grade 3, invasive mechanical ventilation.
- Grade 3 BPD at 36w PMA according to the Jensen et al. (2019) definition
- Use of postnatal steroids for treatment of evolving chronic lung disease (separate from study drug) from 7 days post final dose of study drug through 36w PMA
- Severe neurodevelopmental impairment (NDI) assessed at 2-year follow-up (22-26 months (mo) corrected age (CA))
- Death by 2-year follow-up (22-26 mo CA)
- Severe NDI or death as assessed at 2-year follow-up (22-26 mo CA)

Analyses will be based on the intention-to-treat principle, unless specified otherwise.

3.3. BACKGROUND AND RATIONALE

Preterm birth is one of the leading causes of neonatal death worldwide (0.97 million, ~35% of all neonatal deaths) (1, 2). Approximately 1 in 8 births in the United States are preterm (3). Preterm infants are at greater risk for mortality and morbidity. There are increased emotional and economic costs to families and implications for public-sector services such as educational, health insurance, and social support systems (3). The annual societal economic burden associated with preterm birth in the US was conservatively estimated to be at least $26.2 billion in 2005 (3). Overall, of extremely preterm (22-28 weeks gestational age and 401-1500g birth weight) infants,

93% develop respiratory distress syndrome, 68% bronchopulmonary dysplasia, 16% severe intraventricular hemorrhage, and 36% late-onset sepsis (4).

In the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) Neonatal Research Network (NRN) in 2014, 20% of the infants enrolled (overall) in the Generic Database (GDB) died (8% by <12h, 12% between 12h-120d, and 1% at >120d) and 47% of infants who survived to 36 weeks developed physiologic BPD (GDB 2014 data). BPD is therefore one of the most common morbidities in preterm infants. Death is a competing outcome for BPD, as infants who die before ascertainment of BPD at 36w PMA cannot be diagnosed with BPD even though they may be at the highest risk. BPD is associated with worse cognitive outcomes in school age (5) and with abnormal pulmonary function in adolescence (6) and adulthood (7). Other than CPAP in the delivery room (8), vitamin A (9, 10) and caffeine (11), few interventions other than postnatal steroids have been shown to be successful in reducing BPD/death in large randomized trials. However, use of postnatal steroids is generally minimized due to concerns of neurodevelopmental impairment.

Preclinical studies:
Surfactant has been used to deliver steroid to the lungs and has been shown to reduce lung inflammation, improve gas exchange, and improve lung histology in animal models of RDS (12-16). Fajardo et al. (12) compared [3H]budesonide in either 0.9% saline or surfactant, administered through an endotracheal tube in a ventilated rabbit model of lung lavage (to mimic surfactant deficiency). Lung samples were analyzed by both autoradiography (alveolar versus airway distribution) and liquid scintillation counting (central versus peripheral deposition). Alveolar and peripheral areas received less (4-11%) of the drug than central tissue (14-28%), and this was not affected by altered lung compliance or by vehicle (surfactant vs. saline)(12). Nimmo al. (13) evaluated dexamethasone added to commercial surfactant (Survanta), and found that surface properties of surfactant were not altered, with good distribution throughout all lobes of the lung. Chen et al. (14) evaluated dexamethasone administered with Survanta in a rat acute lung injury model, and found that the dexamethasone/Survanta combination improved gas exchange, lung volumes, and reduced inflammatory cell infiltrate compared to controls.

Ricci et al.(15) evaluated in vitro characteristics and in vivo safety and efficacy of the combination of budesonide and poractant alfa. The chemical stability of budesonide dispersed within poractant alfa over 24 h was demonstrated using HPLC-UV analysis. No significant difference in the content of budesonide was observed during the 24-h incubation at room temperature. Neither poractant alfa alone nor poractant alfa supplemented with budesonide showed significant changes in viscosity after incubation. Wilhelmy Balance tests indicated that budesonide supplementation did not inhibit poractant alfa surface tension activity. The addition of budesonide to poractant alfa did not affect the physiological response to surfactant treatment in RDS animal models (preterm rabbits and surfactant depleted adult rabbits), and was associated to a significant reduction of lung inflammation in surfactant-depleted rabbits (15). Cimato et al found that glucocorticoids have a ceiling of incorporation in surfactant of around 10wt%, and the glucocorticoids not incorporated remains as crystals in the aqueous phase without altering the biophysical properties of the surfactant (17).

Roberts et al.(18) evaluated the pharmacokinetics of 0.25 mg/kg budesonide administered with surfactant in five preterm lambs. Plasma and tissue samples were taken from the lambs for measurement of budesonide, 16α- hydroxy prednisolone, and budesonide palmitate. Peak plasma budesonide concentrations were inversely correlated with the oxygenation index (correlation coefficient of -0.75). The apparent clearance and apparent volume of distribution of budesonide were 6.29 L/h (1.99 L/h/kg) and 29.1 L (9.2 L/kg), respectively. Budesonide and budesonide palmitate, but not 16α-hydroxy prednisolone, were detected in lung tissue. In this study, budesonide and its metabolites were not detected in the brain, which suggests that after local pulmonary deposition by intratracheal instillation, there is no evidence of budesonide accumulation in the central nervous system (18).

Kothe et al determined the effects of budesonide and surfactant on mechanical –ventilation induced lung injury in preterm lambs (19). In this study, preterm lamb fetuses at 125d GA (term =150d GA) were randomized to either a) mechanical ventilation with escalating VT to target 15 mL/kg by 15 min or b) continuous positive airway pressure (CPAP) of 5 cmH2O. After the 15 min intervention, lambs were given surfactant 100 mg/kg with 1) saline, 2) budesonide 0.25 mg/kg, or 3) budesonide 1 mg/kg. The fetuses were returned to the uterus for 24 hours, then delivered and ventilated for 30 min to assess lung function. It was observed that budesonide levels were low in lung (19+2 ng/g in CPAP + budesonide 0.25 mg/kg and 24 + 5 ng/g for Fetal invasive mechanical ventilation + budesonide 0.25 mg/kg) and plasma (0.2+0.04 ng/mL in CPAP + budesonide 0.25 mg/kg and 0.2+0.02 ng/g for Fetal invasive mechanical ventilation + budesonide 0.25 mg/kg). CPAP groups had improved oxygenation, ventilation, and decreased injury markers compared to fetal invasive mechanical ventilation lambs. Budesonide improved ventilation in CPAP lambs. Budesonide decreased lung weights and lung liquid, and increased lung compliance and surfactant protein mRNA. Budesonide decreased pro-inflammatory and acute phase responses in lung. Airway thickness increased in animals not receiving budesonide. Systemically, budesonide decreased MCP-1 mRNA and preserved glycogen in liver. Budesonide 0.25 and 1 mg/kg were similar in these effects (19). Hillman et al. (20) also showed in this mechanical-ventilation induced lung injury model in lambs that budesonide decreased lung inflammation, and decreased pro-inflammatory cytokine mRNA in the lung, liver, and brain to levels similar to those in lambs ventilated with normal tidal volume. This indicates that the budesonide may have systemic anti-inflammatory effects that may potentially be beneficial.

The admixture of budesonide with surfactant has been shown not to reduce surfactant function (15, 21, 22). Budesonide potency, stability, and anti-inflammatory effects have been evaluated in explants of second trimester human fetal lung by Barrette et al. (23). Budesonide suppressed chemokines IL-8 and CCL2 (MCP-1) within 4 hours, reaching a 90% decrease at 12 hours, which was fully reversed 72 hours after removal of the steroid. Half-maximal effects occurred at 0.04-0.05 nM, a fivefold greater potency than for dexamethasone. Budesonide significantly induced 3.6% and repressed 2.8% of 14,500 sequenced mRNAs. Budesonide retained activity in the presence of surfactant and did not alter its surface properties. There was some formation of palmitate-budesonide in lung tissue but no detectable metabolism to inactive 16α-hydroxy prednisolone (23).

Human studies:
A pilot trial by investigators in Taiwan (Yeh et al.) (21) on 116 VLBW infants born between 2004 and 2006 with severe RDS (requiring invasive mechanical ventilation with $FiO_2 \geq 0.6$ shortly after birth) found that a combination of budesonide with surfactant led to lower BPD/death at 36w (19 of 60 in treatment group vs. 34 of 56 in control group) with no significant adverse effects. In this study, blood samples for pharmacokinetic studies were obtained in 22 infants – 10 in the treated group and 12 controls. The peak plasma concentration of budesonide was seen at ~30 minutes, and the peak of 16alpha-hydroxyprednisolone was at 2 hours after instillation (21). The terminal half-life was 4.13 hours, with the AUC of budesonide from 0-8h of 115.73 ng/mL. It was calculated that the total amount of budesonide in the blood (assuming a blood volume of 80 mL/kg) was 9258 ng, which would consist of ~4% of the budesonide instilled into the lung. There were no significant differences between treatment and control groups in plasma cortisol levels (21).

Recently, exciting new data from the same Taiwanese group of investigators have indicated that a combination of a glucocorticoid (budesonide) co-administered with surfactant (Survanta) is able to substantially reduce BPD/death (24). In this study, 256 VLBW infants born between 2009 and 2013 who received invasive mechanical ventilation with $FiO_2 \geq 0.5$ within 4h of birth were randomized to either surfactant + budesonide (100 mg/kg surfactant + 0.25 mg/kg budesonide; n=131) or only surfactant (n=134). It was observed that infants who received surfactant + budesonide had a lower incidence of BPD/death (55 of 131 or 42% vs. 89 of 134 or 66%; relative risk (RR) 0.58, 95% CI 0.44-0.77; NNT 4.1, 95% CI 2.8–7.8). The surfactant + budesonide group required significantly fewer doses of surfactant than did the surfactant-only group (64.9% with only one dose in surfactant + budesonide group vs. 36.6% in surfactant-only group, $p<0.001$). The surfactant + budesonide group also had significantly lower interleukin levels (IL-1, IL-6, IL-8) in tracheal aspirates at 12 hours and lower IL-8 at 3–5 and 7–8 days(24). At follow-up, 85 infants in the surfactant + budesonide group were compared to 87 infants in the surfactant-only group, and favorable trends were noted for NDI (30.6% in surfactant + budesonide group vs. 39.1% in surfactant-only group) with similar weight and length in both groups (24).

A small randomized trial in China by Pan et al. (25) evaluated 30 VLBW infants who were randomly assigned to either surfactant + budesonide or surfactant alone. It is reported that the surfactant + budesonide group had a lower incidence of BPD, shorter duration of mechanical ventilation and shorter duration of oxygen supplementation, although the sample size was very limited (25).

A meta-analysis by Venkataraman et al. (26) of the two randomized controlled trials (RCT) by Yeh (21, 24), and a review by Hascoet et al. (27) are consistent with the view that the use of surfactant as a vehicle for budesonide may reduce the risk of BPD. In the meta-analysis, infants who received intra-tracheal instillation of budesonide-surfactant mixture demonstrated a 43% reduction in the risk of BPD (RR: 0.57; 95%CI: 0.43-0.76, NNT = 5). Mortality was not statistically different between the groups (OR: 0.61; 95%CI: 0.34-1.04), and a 40% reduction was observed in the composite outcome of death or BPD in the budesonide-surfactant group (RR: 0.60; 95%CI: 0.49-0.74, NNT = 3) (26).

Kothe et al. (28) performed a retrospective cohort study of the combination of budesonide with surfactant. In August 2016 their level IV neonatal intensive care unit (NICU) began administering budesonide (0.25 mg/kg) mixed with surfactant (Survanta 4 mL/kg) to all infants ≤ 1250 grams who failed CPAP and required intubation. Infants with congenital anomalies, GA less than 23 weeks, or birth weight less than 500 grams were excluded. Infants were compared to a historical cohort (2013 to 2016) who received surfactant alone. The combination was mixed at bedside or by the transport team, and administered in a similar fashion and for similar indications as routine surfactant therapy. The infants receiving budesonide had a median birth weight of 850g and gestational age of 26.7 weeks (Table 1). It was observed that BPD or death did not change between the historical surfactant cohort (71%, n=294) and the budesonide cohort (69%, n=173) (Table 2). However, budesonide was associated with a decrease in the need for continued mechanical ventilation, severe BPD type II or death (19% to 12%), grade III BPD or death (31% to 21%) (Table 2). Histologic chorioamnionitis was associated with decreased budesonide effects. Secondary morbidities (NEC, IVH, ROP, Sepsis) were similar (Table 3) and the median gestational age at discharge was one week earlier (Table 4). This retrospective cohort study provides some reassuring data regarding short-term safety. As severe BPD was reduced with budesonide, it is possible that there may be potential benefits due to reduction of postnatal steroid use, and lower rates of neurodevelopmental impairment (due to reduction in severe BPD and in use of postnatal steroids).

Table 1 Demographics of Cohorts

	Surfactant	**Surfactant + Budesonide**	**p-value**
Dates of cohorts	8/1/2013 to 7/31/2016	8/1/16 to 7/31/18	
Infants in cohort	294	173	
Gestational Age (Mean)	26.7 ± 2.1	26.7 ± 2.1	0.71
Gestational Age (Median)	26.4 (25.0, 28.1)	26.7 (25.0, 28.4)	0.55
Birth Weight (Mean)	846 ± 205	863 ± 214	0.39
Birth Weight (Median)	825 g (674 g, 1020 g)	850 g (680 g, 1070 g)	0.43
Male	53% (156/294)	56% (96/173)	0.61
Caucasian	41% (123/294)	38% (65/173)	0.38
Outborn Infants	18% (53/294)	16% (27/173)	0.52
Antenatal Steroids	83% (243/294)	80% (139/173)	0.54
Chorioamnionitis	57% (157/274)	51% (76/150)	0.19
Apgar 5 min	6.2 ± 1.9	6.4 ± 1.8	0.23
CRIB II Score (Mean)	10.4 ± 3.0	10.5 ± 2.8	0.87
CRIB II Score (Median)	10.5 (8, 13)	10 (9, 12)	0.95
Surfactant Doses (Mean)	1.94 ± 0.5	2.06 ± 0.73	0.053
Surfactant Doses (Median)	2 (2, 2)	2 (2, 2)	0.14

Mean ± SD; % (infants with condition/infants with results available). Median (25%, 75%)

Table 2 Respiratory Outcomes of Cohorts

	Surfactant	Surfactant + Budesonide	p-value
DOL #7			
InvMV/HFOV	48% (135/280)	34% (57/166)	**<0.01#**
NIPPV	15% (42/280)	16% (26/166)	0.89
CPAP	36% (100/280)	49% (81/166)	**<0.01#**
Average FiO_2	0.31±0.12	0.30±0.11	0.12
NICHD BPD Calculator Average	57±26	52±27	0.06
NICHD BPD Calculator ≥ 60%	55% (155/280)	45% (74/166)	**0.03#**
Postnatal Dexamethasone	51% (150/294)	42% (73/173)	0.07
36 Weeks Corrected Gestational Age			
InvMV/NIPPV	10% (26/263)	3% (5/158)	**0.01#**
CPAP	33% (86/263)	29% (46/158)	0.45
Nasal Cannula or Room Air	57% (151/263)	68% (107/158)	**0.04#**
Death	11% (31/294)	9% (15/173)	0.52
NICHD BPD definition			
No or Mild BPD	29% (86/294)	31% (53/173)	0.75
Moderate BPD	4% (12/294)	4% (7/173)	1.0
Severe BPD Type I	47% (139/294)	54% (93/173)	0.18
Severe BPD Type II	9% (26/294)	3% (5/173)	**0.02#**
Moderate/Severe BPD/Death	71% (208/294)	69% (120/173)	0.75
Severe Type II BPD or Death	19% (57/294)	12% (20/173)	**0.03#**
NICHD BPD Workshop Grading 2018			
No BPD	29% (85/294)	31% (53/173)	0.75
Grade 1	14% (41/294)	9% (15/173)	0.18
Grade 2	26% (77/294)	40% (69/173)	**<0.01#**
Grade 3	20% (31/294)	12% (21/173)	**0.02#**
Grade 3 or Death	31% (91/294)	21% (36/173)	**0.02#**

Mean ± SD; % (infants with condition/infants with results available)

InvMV: Invasive Mechanical Ventilation; NIPPV: Non-Invasive Positive Pressure Ventilation

* $p<0.05$ with t-test; # $p<0.05$ with chi-square test; t $p<0.05$ with Mann-Whitney U test

Table 3 Neonatal Morbidities of Cohorts

	Surfactant	Surfactant + Budesonide	p-value
NEC ≥ Bell Stage 2	7% (21/294)	6% (11/173)	0.75
Isolated Perforation	4% (12/294)	4% (7/173)	0.99
Blood culture positive sepsis	11% (32/294)	10% (17/173)	0.84
IVH: Grade III or IV	16% (48/294)	16% (27/173)	0.84
PVL on HUS or MRI	5% (15/294)	6% (10/173)	0.74
VP Shunt or Reservoir	4% (12/294)	5% (8/173)	0.78
ROP ≥ Stage 2	18% (52/294)	15% (26/173)	0.46
ROP Treatment	6% (18/294)	6% (11/173)	0.87
PDA on any Echocardiogram	63% (185/294)	52% (90/173)	**0.02#**
Medical Treatment for PDA	35% (102/294)	22% (38/173)	**<0.01#**
PDA Ligation	10% (28/294)	3% (5/173)	**<0.01#**
Pneumothorax	7% (22/294)	6% (11/173)	0.71
Pulmonary Hemorrhage	15% (44/294)	9% (16/173)	0.08
PIE	18% (54/294)	21% (36/173)	0.50
Sildenafil for PHTN	6% (17/294)	3% (6/173)	0.26
Insulin for hyperglycemia	24% (70/294)	21% (37/173)	0.62

Mean ± SD; % (infants with condition/infants with results available)

NEC: Necrotizing Enterocolitis; IVH: Intraventricular Hemorrhage; PVL: Periventricular Leukomalacia;

VP: Ventriculoperitoneal Shunt; PDA: Patent Ductus Arteriosus; PIE: Pulmonary Interstitial Emphysema

* p<0.05 with t-test; # p <0.05 with chi-square test; t p<0.05 with Mann-Whitney U test

Table 4 Length of Stay, Discharge Statistics

	Surfactant	Surfactant + Budesonide	p-value
Median LOS	94 (75-118) days	89 (66.5-113) days	0.06
Median GA at Discharge	40.0 (38.1-43.0) wk	39.0 (37.2-41.9) wk	**<0.01t**
Death	10.5% (31/294)	8.7% (15/173)	0.53
Nasal Cannula at Discharge	46% (122/263)	47% (75/158)	0.84
Tracheostomy Placement	3.0% (8/263)	2.5% (4/158)	0.99
HFOV during hospitalization	44% (130/294)	31% (54/173)	**<0.01#**
GA at Last NG Feed (Mean)	38.3 ± 4.5 wk	38.1 ± 4.2 wk	0.66
GA at Last NG Feed (Median)	37.6 (35.9, 39.7) wk	37.1 (35.6, 38.9) wk	0.29
GA at Last Apnea (Mean)	37.3 ± 4.4 wk	37.6 ± 4.7 wk	0.61
GA at Last Apnea (Median)	37.0 (35.1, 39.0) wk	36.9 (35.1, 39.0) wk	0.77
GA Apnea or NG (Mean)	39.5 ± 4.6 wk	39.0 ± 4.9 wk	0.41
GA Apnea or NG (Median)	38.6 (36.8, 41.0) wk	37.9 (36.1, 40.6) wk	0.052
Gastrostomy Tube Placement	8% (20/262)	4% (6/167)	0.11
Weight Gain/Day (grams)	23.9 ± 3.9 g	23.9 ± 3.6 g	0.95
Length Gain/Day (cm)	0.13 ± 0.03 cm	0.14 ± 0.03 cm	**<0.01***
2 or more risk factors for poor neurodevelopment or death	23.5% (69/294)	22.0% (38/173)	0.79

Mean ± SD; Median (IQR); % (infants with condition/infants with results available)

LOS: Length of Stay; GA: Gestational Age

* p<0.05 with t-test; # p <0.05 with chi-square test; t p<0.05 with Mann-Whitney U test

The directly instilled dose of budesonide (0.25 mg/kg) used by Yeh et al.(24) may possibly be higher than needed for maximal effect, and it is unclear how many doses are optimal, as it is possible that too many doses may inhibit lung development. Our collaborators Drs. Roberta and Phil Ballard (UCSF) and Dr. Cindy McEvoy (OHSU) engaged in a dose-ranging study (NCT 02907593) in extremely preterm infants funded by the Thrasher foundation and with an IND (IND # 128102) from the FDA to evaluate doses ranging upwards stepwise from 0.025 mg/kg to 0.1 mg/kg on respiratory illness severity, cytokines, and clinical outcomes at day 28 and 36w PMA, which was published recently in Pediatric Research (29). Twenty-four infants with mean gestational age 25.0 weeks and 743 g birth weight requiring mechanical ventilation were enrolled at mean age of 6 days. Budesonide was detected in the blood of all infants with a half-life of 3.4 h. Treatment was associated with a sustained decrease (mean 65%) in tracheal aspirate cytokine levels at all three dosing levels in some, but not all, infants. There were time- and dose-dependent decreases in blood cortisol concentrations and changes in total blood metabolites. However, respiratory outcomes did not differ from the historic controls (29). The average number of doses was 4 (range 2-5), and hence infants receiving the 0.1 mg/kg dose received a total budesonide dose of 0.4 mg/kg. However, they did not evaluate the dose of 0.25 mg/kg, and their study did not have concurrent controls nor was it powered to detect significant differences in clinical outcomes (29). In personal communication with the lead author Dr. Cindy McEvoy, there were no SAEs considered treatment related. The one SAE at 0.025 mg dose was severe respiratory decompensation, one SAE at 0.05 mg dose was sepsis with prolonged antibiotics, and at the dose of 0.1 mg, there was severe respiratory decompensation and NEC in one patient, and sepsis in another patient. These events are frequent in mechanically ventilated preterm infants.

The randomized trials of budesonide + surfactant to date (21, 24) and the observational study by Kothe et al.(28) have not identified any major safety concerns related to the use of budesonide, specifically in relation to spontaneous intestinal perforation (SIP). There is however a theoretical safety concern in regards to SIP, for early dexamethasone treatment in a study by Stark et al. (0.15 mg/kg per day x 3 days, starting within 24h of birth, then tapering over a period of 7 days: total dose 0.89 mg/kg) was associated with SIP (13% vs. 4% in placebo; p= 0.02) (30). Currently, in the NICHD NRN, the incidence of SIP is 4% in extremely preterm infants (GDB data, 2018), ranging from 0% to 8% in different centers. However, budesonide in this proposed trial will be given intra-tracheally with low concentrations expected in the blood (21) as compared to systemic administration in the study of early dexamethasone by Stark et al(30). Therefore, SIP as a result of budesonide as used in this trial is possible (given the data with dexamethasone from Stark et al (30)) but unlikely (given the data from the studies to date with budesonide+surfactant). Hence, SIP will be one of the safety outcomes that will be evaluated carefully in this trial.

The NRN is a collaborative network of large neonatal intensive care units with a diverse patient population from multiple regions of the United States and with an existing infrastructure for carrying out large multicenter clinical trials and follow-up in extremely preterm infants, and thus is optimal for such a study.

Similar to the individual patient meta-analyses conducted through the NeoPROM including patients enrolled in SUPPORT, COT, and BOOST trials (31, 32), it is possible that this trial may lend itself to collaboration with other international consortia for individual patient meta-analyses,

such as with the RCT in Australia. We are in contact with Drs. Brett Manley and Omar Kamlin who are organizing the PLUSS RCT in Australia (ACTRN12617000322336p).

SECTION 4. METHODS

4.1. STUDY POPULATION

4.1.1. Inclusion Criteria

To be enrolled in this study, participants must meet all of the following criteria:

- Liveborn infants 22 $^{0}/_{7}$ – 28 $^{6}/_{7}$ weeks gestation or 401 – 1000 grams (inclusive) birth weight,
- Clinical decision to give surfactant, and
- Less than or equal to 48 hours postnatal age (infants must be enrolled into the trial early enough (via either antenatal consent or early postnatal consent) so that randomization can be started in the window of ≤ 48h postnatal age (study drug initiation can occur ≤ 50 hours postnatal age)).

4.1.2. Exclusion Criteria

To be enrolled in this study, participants must not meet any of the following criteria:

- Terminal illness (heart rate < 100 beats per minute, unresponsiveness to resuscitation) or unlikely to survive as judged by the clinician,
- Decision to redirect or limit support,
- Use of surfactant before enrollment (first dose of surfactant must be study drug),
- Infant received systemic steroids prior to enrollment,
- Use of indomethacin, either received by the mother within 24 hours prior to delivery, received by the infant prior to enrollment, or intent to administer to the infant for IVH prophylaxis or PDA management from enrollment up to 7 days of final dose of study drug,
- Serious chromosomal abnormalities or major malformations,
- Known congenital infections including, but not limited to, confirmed sepsis, congenital CMV, etc.,
- Infants with a permanent neuromuscular condition that affects respiration, or
- Enrollment in a conflicting clinical trial.

4.2. DETAILED STUDY PROCEDURES

4.2.1. Screening

Clinical research coordinators will screen pregnant women admitted at 22-28 weeks of gestation who are considered at risk of preterm delivery, and will screen extremely preterm infants admitted to the neonatal intensive care unit for meeting eligibility criteria.

4.2.2. Consent Procedures

Consent can be obtained either before birth of the infant (antenatal consent) or after birth of the infant (postnatal consent), as long as the consent is obtained early enough to assess eligibility and randomize the infant in the trial by 48h of age, so that study drug can be administered within 50h of age.

Infants are eligible to be included within 48h of birth (of other studies and registries performed by the NRN, 97% in the SUPPORT study and 98% in the GDB registry for the first few months of 2016 received the first dose of surfactant within 48h; 91% in the first day, 99% by 72h; 55% in SUPPORT received just 1 dose). Attempts will be made to obtain antenatal consent, but if not possible, postnatal consent will also be sought to maximize enrollment. A +2h grace period will be allotted for attaining and administering the dose (study drug may be administered up to 50h after birth). Of 376 infants in GDB in early 2016 on whom we have data, only 31% received surfactant in the delivery room (DR) although there is likely to be center variation, so two-thirds may receive surfactant later; the rate of BPD/death is 59% in those who received surfactant in the DR vs. 65% in those who received surfactant later, so there does not appear to be a large difference in risk of BPD between DR surfactant and NICU surfactant administration.

All infants enrolled in this study must also be consented and enrolled in the GDB registry, thus all data collected through the GDB registry will be available for this study.

4.2.3. Randomization Procedures

Due to the frequent need to administer surfactant to extremely preterm infants in the delivery room, treatment assignments must be made in an expeditious manner in order to enroll these infants in the study, while also maintaining balanced allocation of the infants to the two treatment arms. If these infants are not enrolled because of time constraints in the delivery room, then inferences may not be generalizable to such infants and enrollment may become unacceptably slow.

To address this issue, the BiB trial adapts the step-forward randomization idea of "Use Next" drug kits, which was originally presented by Zhao et al. (33). Based on a randomization schedule centrally generated by the NRN Data Coordinating Center (DCC) at RTI, drug kits of budesonide respules or sham will be randomized, assembled, masked, and labeled by the Investigational Drug/Research Pharmacy at each site, then stored in a locked location that will allow for rapid access by the respiratory therapist (or other qualified designated person). Drug kits will be added to the queue such that there are at least three sets of kits available in each gestational age stratum at a given time, and the Investigational Drug/Research Pharmacy will be responsible for ordering, stocking, and supplying the respules of budesonide and sham to the NICU in the drug kits. Two drug kits will be prepared for each randomization number in case of the need for a second dose of study drug within the treatment window, thus a set of drug kits includes two drug kits. Curosurf will be available as clinical supply and separate from the drug kits. As dosing for budesonide may require two respules (in case of accidental spill/drop), at least two respules of budesonide (or sham) will be included in each drug kit, for a total of four respules in a set of drug kits (i.e., four respules per randomization ID).

In addition to labeling the drug kits with the required cautionary statement that the drug product is only for investigational purposes, the sequential randomization number will also be labeled on each kit, such that the designated person (e.g., respiratory therapist) will select the next sequential randomization number in the queue. If eligible multiple births are expected, then the corresponding number of kits will be taken from the queue in the randomization number ordering, as multiple gestation births will be randomized independently. Infants will be considered randomized and assigned to the randomization number when the masked drug kit is opened, which will occur after assessment of eligibility and directly before treatment administration. If the drug kit is not opened, then it may be returned to the queue in the locked location and the randomization number is considered unused. The unmasked respiratory therapist (or other qualified designated person) will mix the budesonide or sham with Curosurf and administer it to the infant. The used respules will then be placed back into the masked drug kits with the infant study number. The Investigational Drug/Research Pharmacy will track usage of the Curosurf, budesonide, and sham by evaluating used vials and respules. Other clinical caregivers will therefore remain masked to treatment group allocation. In hospitals where it is necessary that the Investigational Drug/Research Pharmacy prepares the study drug, the Investigational Drug/Research Pharmacist will be unmasked and will prepare and supply the prepared study drug to the NICU for administration by the masked respiratory therapist. Further details about the implementation of the randomization strategy can be found in the Manual of Operations.

Due to the need for physical queues of randomized study drug for rapid access, 1:1 randomization to the budesonide + surfactant arm or the surfactant alone arm will be stratified by NRN site (NICU) and gestational age (<26 weeks vs. ≥26 weeks) via the block urn design with a stratum-specific maximum tolerable imbalance known to the DCC. The block urn design was proposed by Zhao and Weng (34) as a modification of the urn design and alternative to the permuted block design in order to maintain consistent imbalance control under the maximum tolerable imbalance between treatment groups, while also lowering the probabilities of deterministic assignments. By having lower probabilities of deterministic assignments than the stratified permuted block design, the block urn design decreases the probability of correct guessing, and thus inadvertent unmasking of research staff and possible selection bias.

4.2.4. Study Intervention and Comparison

Infants randomized to the active control arm will receive a dose of surfactant (poractant alfa; Curosurf 2.5 ml/kg) while infants randomized to the intervention arm will receive a dose of surfactant mixed with budesonide (Pulmicort nebulizing suspension or equivalent generic). The dose of budesonide will be 0.25 mg/kg in a volume of 1 ml/kg, for a total volume of 2.5 ml/kg of Curosurf + 1 ml/kg of budesonide. If the infant is to receive the second dose of study drug, the dosage of Curosurf will be 1.25 ml/kg for the second dose (noting that the first dose of Curosurf is 2.5 ml/kg, regardless of whether a second dose is anticipated or not).

Using an aseptic field, each drug is drawn up by a trained individual (respiratory therapist, pharmacist, nurse, or physician) using aseptic technique from the Curosurf vial (3 or 5 mL syringe) and budesonide respule (1 mL syringe). The budesonide is then injected into the larger syringe using a connector, and the syringe is inverted a few times to mix the two. The syringe is then covered in a label (to hide appearance and volume) and then taken to the patient and is

inverted a few more times before administration into the endotracheal tube in the standard manner for surfactant.

It is planned that the study drug will be administered soon after preparation, although stability and surface-tension lowering ability of the budesonide + surfactant combination should last for at least 24 hours.

The study drug will be administered for at least one dose to infants who meet criteria for surfactant administration, and for a maximum of two doses. After 50h of life, subsequent uses and type of surfactant will not be directed by study protocol but will be by clinician preference and center practice. The exact process of surfactant administration (size of aliquot, infant positioning, etc.) will be as per clinician preference and center practice.

Surfactant use will be standardized on Curosurf (of 23 NICUs responding to a survey on surfactant use, 13 use Curosurf, 7 Infasurf, and 7 Survanta – some use more than one; when asked if the study decides to use a single type, 17 NICUs were willing to use standard study surfactant, 3 were not willing – these 3 sites (NICUs) are from a single center and use Curosurf already and do not want to switch). An optional second dose of study drug may be administered, provided the second dose would be administered within 48+2 hours of birth.

Suggested criteria for the initial dose of surfactant includes intubation of the infant with FiO_2 > 0.25 to maintain SpO_2 > 90%, or a $PaCO_2$ > 65 torr at < 48h age. Suggested criteria for a second (repeat) dose of study drug includes intubation of the infant at < 48h age with mean airway pressure > 6 cm H_2O and FiO_2 > 0.30 to maintain SpO_2 > 90%, or a $PaCO_2$ > 65 torr.

4.2.5. Blinding/Masking

This study will be masked, and all attempts will be made to maintain masking to the extent possible. Only research pharmacists and a designated respiratory therapist (or other qualified person) will be unmasked at the enrolling NICUs. The designated respiratory therapist (or other qualified person) must be unmasked to allow drug mixing at bedside for expeditious study drug administration; however, this person will not be the primary medical provider nor the primary data collector for that infant, and will not be otherwise involved in the research.

Each NICU's study-certified pharmacist will be responsible for tracking and documentation of study drug kits, as well as reporting directly to the DCC any protocol deviations/violations regarding unmasking on a designated study form.

At the NICUs with bedside mixing, the mask will be preserved through use of drug kits. Drug kits will be prepared with budesonide or sham by the unmasked pharmacist and will be fully masked from the exterior in order to maintain masking of clinicians, research personnel, and families. The designated respiratory therapist (or other qualified person) will not know the randomized treatment arm prior to opening the drug kit. Once opened, the budesonide should be mixed (or sham mimed to be mixed) with the surfactant by the same unmasked person. Mixing and administration should occur reasonably out of sight from masked individuals, and if needed, masking tape may be used to hide the total volume of the syringe used to administer the mixture (budesonide does not change the appearance of the surfactant solution, although the volume is slightly higher when budesonide is added). Before intratracheal instillation, the syringe will be

gently mixed (not shaken) by inverting the syringe, and the surfactant or surfactant + budesonide mixture will be administered in a manner similar to that of routine surfactant therapy. Once the kit is spent, all masked contents of the kit will be returned to the kit, which is resealed and returned to pharmacy for end processing. The randomization ID tied to a kit does not include a coded randomization assignment.

Additional logistical discussion of the masking process is discussed in the Manual of Operations.

4.2.6. Control or Monitoring of Co-interventions

Early (< 7 days after the last dose of study drug) postnatal systemic steroids will be discouraged and reserved only for infants (at clinician discretion) who have fluid-resistant hypotension OR vasopressor-resistant hypotension, OR evidence of hyponatremia and low serum cortisol concentrations (as per local NICU definitions, with suggested definitions including: fluid resistant hypotension defined as receiving 20 ml/kg or more of fluid infusion for hypotension in < 2 hours; vasopressor resistant hypotension defined as receipt of treatment with at least one vasopressor at a higher dose such as dopamine at 10 mcg/kg/min or more).

The use of postnatal steroids at later time points will be considered a secondary outcome and it is suggested that use of postnatal systemic steroids not exceed the dosing used in DART or the Hydrocortisone trial (if hydrocortisone is used), except in patients with demonstrated adrenal insufficiency.

Other co-interventions (e.g. use of ibuprofen or other agents for PDA management) are permissible as per clinician preference or unit practice, although such use would be recorded in this pragmatic trial. However, prophylactic or therapeutic use of indomethacin during the seven days following the last dose of study drug is not permissible in this study due to the possibility of increased risk for SIP. All reportable, concomitant medications will be collected and summarized.

A comprehensive safety and efficacy evaluation will be performed for this trial, including outcomes listed below in Sections 4.2.7 - 4.2.10. All safety variables will be evaluated prospectively. The enrolled infants are extremely premature infants admitted to the neonatal intensive care unit, and are routinely monitored by a team of highly trained physicians and nursing staff, usually with continuous monitoring of heart rate, pulse oximetry, respiratory rate, temperature, and other vital signs at frequent intervals. The safety parameters being monitored are part of the routine clinical monitoring in all participating NICUs (standard of care for neonatal intensive care).

4.2.7. Primary Outcome

The primary outcome is physiologic BPD or death by 36 weeks' post-menstrual age in all randomized extremely preterm infants and will be recorded by the Research Coordinator at participating centers, using existing GDB criteria.

4.2.8. Secondary Outcomes

The following secondary outcomes will be assessed for all randomized subjects, with many being standard in the NRN:

- Death by 36w PMA
- Physiologic BPD at 36w PMA
- BPD severity as defined by Jensen et al. (2019) (35) at 36w PMA according to treatment with the following support:
    - No BPD, room air;
    - Grade 1, nasal cannula at flow rates ≤ 2 L/min;
    - Grade 2, nasal cannula at flow rates > 2 L/min or noninvasive positive airway pressure;
    - Grade 3, invasive mechanical ventilation.
- Grade 3 BPD at 36w PMA according to the Jensen et al. (2019) definition
- Use of postnatal steroids for treatment of evolving chronic lung disease from 7 days post final dose of study drug through 36w PMA
- Severe NDI assessed at 2-year follow-up (22-26 months corrected age). In light of the upcoming transition to BSID IV, severe NDI assessment will be based on the agreed-upon definition at the time of the first participant's follow-up assessment. An example of such a definition could be presence of any of the following (36):
    - Cognitive composite score on the BSID IV < 70,
    - GMFCS level 3-5,
    - Severe hearing impairment (no functional hearing despite amplification), or
    - Bilateral severe visual impairment (bilateral blindness despite correction).
- Death by 2-year follow-up (22-26 months corrected age)
- Severe NDI or death as assessed at 2-year follow-up (22-26 months corrected age)

4.2.9. Exploratory Outcomes

The following exploratory outcomes will be collected for all randomized subjects:

- BPD severity (none/mild/moderate/severe) by the NIH (NICHD/NHLBI June 2000 Workshop) definition at 36w PMA (37)
- Number of days on invasive mechanical ventilation by postnatal day 28
- Number of days on invasive mechanical ventilation by 36w PMA
- Intubation after the treatment window (50h postnatal age) and within the first 28 postnatal days
- Intubation after the treatment window (50h postnatal age) and within 36w PMA
- Administration of repeat surfactant doses after the treatment window (50h postnatal age) and within 7 days after last dose of study drug

- Reported respiratory outcomes as assessed at 2 year follow-up (22-26 months corrected age), specifically:
    - Recurrent wheezing
    - Chronic coughing

Possible ancillary studies will evaluate development/analysis of a biorepository (genomic/proteomic analysis, similar to the Cytokine study) in this cohort.

4.2.10. Safety Outcomes

Adverse events (AEs) are monitored during the study (from treatment initiation through 7 days (168 hours) post final study drug administration) for all AEs, and then continuous monitoring within 30 days of final study drug administration for specified AEs (e.g., spontaneous intestinal perforation). The following are pre-specified events to be monitored (see Appendix A Toxicity Table Severity/Intensity Grading Scale of the Manual of Operations for specific diagnostic and grading criteria):

- Within 7 days of final study drug administration:
    i. Hyperglycemia
    ii. Hypertension
    iii. Prolonged hypoxemia with bradycardia
    iv. Endotracheal tube blockage
    v. Any other adverse event deemed moderate or worse in severity. Mild events are not recorded unless the event is also considered unexpected.
- Within 30 days of final study drug administration:
    i. Spontaneous intestinal perforation (SIP)

All serious adverse events (SAE) and those events requiring IND safety reporting will be followed until satisfactory resolution or until the site investigator deems the event to be chronic or the adherence to be stable or by study status of 36 weeks' post-menstrual age.

Neonatal morbidities and outcomes occurring during the study-defined AE monitoring period are captured as an AE and recorded in lesser detail in the NRN Generic Database (GDB). The following list denotes additional pre-specified events to be monitored, however, these outcomes are deemed to be risks of prematurity, and therefore possible, but unlikely to be related to study intervention. Specific diagnostic and grading criteria for these events can also be found in Appendix A Toxicity Table Severity/Intensity Grading Scale of the Manual of Operations.

- Within 7 days of final study drug administration:
    i. Hypotension
    ii. Pulmonary air leak
    iii. Culture positive sepsis (early-onset sepsis or late-onset sepsis)

iv. Intracranial hemorrhage (with allowance for a three-day grace period to receive a head ultrasound)

- Within 30 days of final study drug administration:
  i. Periventricular leukomalacia (PVL)

Neonatal morbidities and outcomes occurring after the study-defined AE monitoring period are also recorded in the GDB in lesser details. Impairment of growth parameters (weight, length, head circumference) at 36 weeks PMA will also be collected and summarized from the GDB.

4.2.11. Compliance Monitoring

Other than study intervention and restricted use of postnatal systemic corticosteroids, other clinical practices are per usual clinical protocol and clinician preference at the site.

4.2.12. Study Specimens

None specifically for this study, although possible ancillary studies may be planned for evaluating tracheal aspirates, blood, and urine for genomic, transcriptomic, microbiomic, and other biomarkers (e.g. inflammatory markers) associated with BPD and other outcomes (e.g., NDI, BPD/death).

4.2.13. Post-hospital Procedures

None

4.2.14. Two Year Follow-up at 22-26 Months Corrected Age

In addition to the usual NRN 2 year follow-up at 22-26 months corrected age for evaluation of NDI, long-term respiratory outcomes will be collected in order to evaluate early childhood pulmonary outcomes, specifically, recurrent wheezing and chronic coughing. The family also will be provided with a summary of the results of the developmental follow-up per center-specific IRB guidelines.

4.2.15. Additional Follow-up Assessments

Funding may be sought for the 5-6-year outcomes assessment, similar to SUPPORT.

4.3. POTENTIAL RISKS AND BENEFITS TO SUBJECTS

All sexes and racial and ethnic groups will be eligible for inclusion. IRB approval will be obtained prior to study implementation, and parental consent will be obtained prior to individual randomization. Confidentiality will be maintained with standard Network practices. Safety monitoring will be performed as outlined. Potential risks include adverse effects of glucocorticoids (short-term effects such as hyperglycemia and hypertension, long-term effects on neurodevelopment), and benefits include reduction of inflammation and BPD with glucocorticoids. A potential short-term adverse effect (possible but unlikely) is an increased risk of SIP in the first week after birth, and hence use of indomethacin will be an exclusion criterion, and indomethacin will be avoided for the first seven days following the last dose of study drug due to this potential theoretical risk. The two RCTs done so far (21, 24) indicate that budesonide at 0.25 mg/kg dose + surfactant is as safe as surfactant alone, with efficacy in reducing BPD. The

retrospective analysis by Kothe et al. (28)also suggests benefits in reduction of severe BPD by budesonide at 0.25 mg/kg dose + surfactant. The literature also indicates that there are no adverse effects on neurodevelopment (the major concern) or growth following budesonide administered with surfactant, and that there may be possible benefit, due to reduction of severe BPD.

However, there are concerns with daily budesonide being used long-term in preterm infants. Bassler et al. (38) performed a randomized controlled trial on 863 infants (23-27w6d) of early (< 24h) daily inhaled budesonide or placebo until they no longer required oxygen or positive pressure support or until they reached a postmenstrual age of 32w. The primary outcome was death or BPD at 36w PMA. It was observed that 40% of infants in the budesonide group died or developed BPD, which was reduced compared to placebo (RR 0.86, 95% CI 0.75-1.00, p=0.05). The incidence of bronchopulmonary dysplasia was 27.8% in the budesonide group versus 38.0% in the placebo group (RR, stratified according to gestational age, 0.74; 95% CI, 0.60 to 0.91; p=0.004); however, death occurred in 16.9% and 13.6% of the patients, respectively (RR, stratified according to gestational age, 1.24; 95% CI, 0.91 to 1.69; p=0.17). The proportion of infants who required surgical closure of a patent ductus arteriosus was lower in the budesonide group than in the placebo group (RR, stratified according to gestational age, 0.55; 95% CI, 0.36 to 0.83; p=0.004), as was the proportion of infants who required reintubation (RR, stratified according to gestational age, 0.58; 95% CI, 0.35 to 0.96; p=0.03). Rates of other neonatal illnesses and adverse events were not different in the two groups, including the occurrence of intestinal perforations (38). It was concluded that the incidence of BPD may be reduced by budesonide, but perhaps at the expense of increased mortality (38). In the long-term (18-22 months) outcome of this trial, it was seen that 48.1% of infants assigned to budesonide had neurodevelopmental disability, as compared with 51.4% of infants assigned to placebo (RR, adjusted for gestational age, 0.93; 95% CI, 0.80 to 1.09; p=0.40). There were more deaths in the budesonide group than in the placebo group (19.9% vs. 14.5% infants; RR, 1.37; 95% CI, 1.01 to 1.86; p=0.04) (39).

It is not clear if the results of the studies by Bassler et al. (38, 39) are applicable to the BiB trial. In the studies by Bassler et al. (38, 39), the dose of budesonide was two puffs (200 μg per puff) administered every 12 hours in the first 14 days of life and one puff administered every 12 hours from day 15 until the last dose of the study drug had been administered. The average duration of budesonide administration was 33.9 days (standard deviation 15.9 days) in the budesonide group. Hence, infants received an approximate total dose of 19.2 mg ([0.4 mg x 2 doses/day x 14 days]+[0.2 mg x 2 doses/day x 20 days]) of budesonide, which is more than 75 times (76.8 times) the dose, and 68 times more frequent (34 days x twice/day) than planned to be used in this study of budesonide with surfactant. Therefore, it is likely that the BiB trial will not see any increase in mortality with budesonide, especially since the meta-analysis (26) indicates a trend towards reduction in mortality with budesonide-surfactant (OR: 0.61; 95%CI: 0.34-1.04) in the two trials so far. Nevertheless, close safety monitoring will be performed by the DSMC and DCC, as described later in the protocol.

SECTION 5. ANALYTICAL PLAN

5.1. STATISTICAL ANALYSIS PLAN

The primary analysis for the primary outcome of death or physiologic BPD by 36 weeks PMA will be assessed by comparing the proportion of infants who died or developed BPD at 36 weeks PMA using a Poisson regression model with variances estimated by the robust sandwich estimator (robust Poisson model) (40, 41). Adjustment for randomization stratification factors study site (NICU) and dichotomous gestational age will be achieved by including these factors as fixed explanatory variables in the model. The primary analysis will be based on the intention-to-treat principle, as will all secondary efficacy analyses in addition to having adjustment for randomization stratification factors, unless otherwise specified. If enrollment at a specific NICU is low, then data from that NICU will be pooled with another NICU belonging to the same NRN center for analysis purposes. Similar consideration will be given to pooling data from NICUs if there are model convergence issues.

Secondary efficacy and safety outcomes will be analyzed via linear regression for continuous outcomes, robust Poisson regression for dichotomous outcomes, Poisson regression for count outcomes, proportional odds models for ordinal outcomes, or generalized logits models for nominal outcomes (with more than two levels). All models will adjust for randomization stratification factors as fixed explanatory variables. Safety analyses will be based on treatment received, such that infants will be considered as belonging to the study arm for which they received treatment, rather than the arm to which they were randomized.

Research staff will work with the DCC for plans to handle missing data and loss to follow-up, with details of those approaches as well as additional details for the models described above included in the SAP that will be finalized prior to review of unmasked data. In addition to basing the analyses on the intention-to-treat principle, pre-specified secondary analyses by treatment received will also be performed, as all infants who are randomized to receive study drug may not receive study drug (infants may stabilize on CPAP and may no longer require surfactant during the interval between randomization and receipt of study drug, or may die during this interval). However, the randomization and study intervention methods aim to minimize this difference in study populations.

5.2. SAMPLE SIZE AND POWER ESTIMATES

The sample size for this study is determined entirely by comparing the surfactant + budesonide arm to the surfactant alone arm for the primary outcome of physiologic BPD or death measured at 36 weeks PMA. Comparisons of secondary outcomes between the study arms will be considered descriptive.

In the NRN, roughly 19% of infants in the GDB do not survive to 36w PMA, and among survivors, 42% are diagnosed with physiologic BPD at 36w PMA, for a combined rate of about 53% for the primary endpoint. Among extremely preterm infants in the GDB (401 – 1000 g birth weight or 22-28w gestational age), these rates are higher: about 24% do not survive to 36w PMA and roughly 45% of survivors develop physiologic BPD by 36w PMA, for a combined rate of about 58% in the target population. It is unlikely that we will see the large magnitude of

reduction (24% absolute risk) seen in the trial by Yeh et al. (24) – it is more likely that we will see a reduction of approximately 10% in absolute risk, from 58% to 48%. It is likely that the outcome will be more common, as we are selecting for the subset of infants who require surfactant. As such, the presented power calculations are conservative in that if the actual risk of BPD or death is greater than 58%, the power associated with an absolute reduction of 10% will be greater than the calculated power.

Assuming the primary outcome of physiologic BPD or death will be analyzed prospectively based on the relative risk for the two treatment arms being different from 1, and that the study will undertake three interim analyses to assess interim efficacy as described in Section 5.5.2.2, Table 5 displays estimates for a sufficient sample size per treatment arm based on large sample methods comparing two proportions.

Table 5 Sample size calculations (*n* per treatment arm)

	Two-sided type I error (α)	
Power	Overall α = 0.05 (Final α = 0.044)	Overall α = 0.01 (Final α = 0.009)
80%	406	593
90%	539	753
95%	664	900

From Table 5, a power of 90% with overall study-wise two-sided type I error of 0.05 (final analysis type I error 0.044 after multiplicity adjustment for the interim analyses), the estimated sample size is 539 per treatment arm, or 1078 total. However, simulation studies for the primary analysis method of the robust Poisson model indicate that a sample size of 550 per group (1100 total) is more accurate to attain 90% power for an overall study-wise type I error of 0.05. Therefore, accounting for approximately 5% attrition for the primary outcome at 36 weeks PMA and randomizing multiple gestation infants independently, the BiB trial will aim to enroll a total of 1160 infants, equally allocated to the two treatment arms.

5.3. AVAILABLE POPULATION

Currently, there are about 2000 extremely preterm infants born annually into the GDB. After applying 10% exclusion for non-viability/malformations and other exclusion criteria, approximately 70% of the remaining 1800 infants will require surfactant (GDB 2017-2018), resulting in 1260 eligible infants per year. Assuming a 33% consent rate due to difficulties with antenatal/early consent (42), the BiB trial can theoretically enroll 415 infants per year, and the required 1160 infants in 2.8 years (1160/415=2.8).

5.4. PROJECTED RECRUITMENT TIME

Enrollment in the trial may be slow, due to issues with antenatal consent and need for research coordinators and parents to be readily available. Based on experience with SUPPORT, it is anticipated that enrollment will require approximately 2.8 years, followed by two additional years for follow-up. It is therefore estimated that the total time required for the study will be: Development and implementation 1 year + enrollment 2.8 years + follow-up 2 years, for a total of five to six years.

5.5. STUDY MONITORING PLAN

5.5.1. Reporting Adverse Events

The target population is of extremely premature infants, who have a very high incidence of mortality and morbidity. The NRN Data Safety Monitoring Committee (DSMC), as a part of their responsibility for reviewing all NRN studies, will evaluate adverse events and safety as well as interim assessments of efficacy and futility.

An **adverse event (AE)** is any untoward medical occurrence in humans, whether or not considered study drug related, which occurs during the conduct of the clinical trial. Any change in clinical status, ECGs, routine labs, x-rays, etc., that is considered clinically significant by the study investigator is considered an AE.

Suspected adverse reaction is any adverse event for which there is a reasonable possibility that the study drug caused the adverse event. A reasonable possibility implies that there is evidence that the study drug caused the event.

Unexpected adverse event or unexpected suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed or is not consistent with the risk information described in the general investigational plan.

Clinical variables of side effects of all medications in the study and any possible unanticipated side effects (any events considered by clinician to be possibly related to study participation, even if a remote possibility) will be recorded.

All adverse events will be monitored from treatment initiation through 168 hours (7 days) after completing study drug administration. Adverse events that are mild in severity, transient, and expected in the study population will not be recorded unless it is considered unexpected. An event that is present at baseline is not considered an AE unless there is an increase in grade (i.e. worsening in severity or frequency) or the event resolves and then returns.

Serious adverse event (SAE): An AE or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include spontaneous intestinal perforation or septicemia within the first postnatal week in enrolled infants. The study clinician will complete an SAE Form within the following timelines:

- All deaths and immediately life-threatening events, whether related or unrelated, will be recorded on the SAE Form and submitted to the DCC and NICHD project scientist within 24 hours of site awareness.

- Other SAEs, regardless of relationship, will be submitted to the DCC and NICHD project scientist within 72 hours of site awareness.

All SAEs will be followed until satisfactory resolution or until the site investigator deems the event to be chronic or the adherence to be stable. Other supporting documentation of the event may be requested by the DCC or NICHD and should be provided as soon as possible. The study medical monitor will be responsible for notifying FDA of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible but in no case later than 7 calendar days after the information is submitted by the clinical site.

5.5.2. Data Monitoring Plan and Stopping Rules

Ongoing analyses by the DCC of the study will focus on study progress and subject safety with three planned formal interim analyses of efficacy. The DSMC will review the progress of the study routinely for adverse events, data quality and completeness, and study accrual, and at specific times for safety, efficacy, and futility using interim monitoring boundaries. The DSMC will review tabular summaries of study data as evidence for changing study procedures or halting the trial, only for reasons relating to the safety of the study subjects or inadequate trial performance (e.g., poor recruitment of subjects). Specifically, when monitoring safety, the DSMC will review the following information:

- Recruitment and overall study progress,
- Randomization to ensure that balance of baseline characteristics is being achieved by randomization,
- Rates of adverse events including serious adverse events, study drug-related adverse events, and deaths, and
- Rates of clinical outcomes.

Additional information on efficacy monitoring, safety monitoring, and futility monitoring is described below, with further details in the SAP.

5.5.2.1. Safety

The DSMC, in collaboration with the DCC, will monitor safety outcomes during interim analyses scheduled after the first 40 infants (~ 3%) have been evaluated for the primary outcome (death or BPD at 36 weeks PMA) or been discharged or transferred, and subsequently after 25%, 50% and 75% of the enrolled patients have reached the same milestone. Formal testing of the incidence of SAEs or death across the surfactant and surfactant + budesonide treatment groups will be assessed based on a Lan-DeMets α-spending function that approximates the Pocock stopping boundary (43). Thus, the adjusted significance level will be 0.0033 at the 3% interim analysis, 0.0196 at 25%, 0.0212 at 50%, 0.0214 at 75%, however, the exact significance level for each interim analysis will depend upon the timing (or more formally the amount of statistical information available at the time) of the analysis and if/when prior analyses have taken place. Thus, at each interim safety look, a p-value less than the corresponding significance level from comparing the incidence of SAEs/death across the groups may be used by the DSMC as evidence of disproportionate harm from the study intervention. For the purpose of formal safety monitoring, SAEs are defined from those safety outcomes specifically listed in Section 4.2.10

falling under the definition of SAE from Section 5.5.1. The formal safety monitoring analysis will be conducted using robust Poisson regression adjusted for site and gestational age strata as fixed effects. Given that there are 15 centers in the NRN, adjustment for site may not be computationally feasible for the first few interim analyses, in which case pooling of sites and/or GLMM with site as a random effect may be explored if adjustment for site is deemed crucial for inference.

An adverse event form will collect the safety information so that it may be entered into the database in a timely fashion. The DSMC will also review tabular summaries of adverse events and study data as supporting evidence to determine whether there are any safety concerns that may impact continuation of the trial.

5.5.2.2. Efficacy

Three formal interim analyses are planned to evaluate the indication of overwhelming early efficacy. Interim analyses will be performed once 25%, 50%, and 75% of total planned enrolled infants reach 36 weeks PMA. To preserve an overall study-wise type I error rate of $\alpha = 0.05$, a Lan-DeMets α-spending function with an O'Brien-Fleming-type stopping boundary will be used The α level will be 0.000015 at 25%, 0.0030 at 50%, 0.0183 at 75%, and 0.0440 at the final analysis. The exact alpha for each interim analysis will depend upon the timing (or more formally, the amount of statistical information available at the time) of the analysis and if/when prior analyses have taken place.

5.5.2.3. Futility

The DSMC at the safety/efficacy looks may evaluate whether the study should be stopped for futility, either because enrollment in the study is proceeding at such a slow pace that the study is unlikely to provide relevant clinical information or because a finding of efficacy is unlikely. As a part of these analyses of unlikely demonstration of efficacy, the DSMC can recommend stopping enrollment for futility if the upper limit of a two-sided 80% confidence interval on the conditional power for the primary test of treatment effect fails to exceed 0.50 at the 50% interim analysis or fails to exceed 0.30 at the 75% interim analysis.

SECTION 6. DATA FORMS

Details regarding data collection are found in either of two study documents 1) Manual of Procedures and 2) Investigational Drug Manual of Procedures (Masked Preparation and Intervention) and contain the follow data collection instruments:

BB01	Screening Log CRF
BB01Ante	Antenatal Screening Log
BB02	Enrollment and Study Drug Initiation CRF
BB03	Respiratory Status/Laboratory Measures CRF
BB04	Concomitant Medicine CRF
BB05	Adverse Event (AE)/Serious Adverse Event (SAE) CRF
BB06	Protocol Violation and Deviation CRF
BB07	Study Withdrawal CRF
BB08a	Unmasked Study Drug Administration (Dose #1) CRF
BB08b	Unmasked Study Drug Administration (Dose #2) CRF
BB09	Pharmacy Drug Accountability CRF
BB010	Follow-Up Respiratory Outcomes CRF

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