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Abstract Title:

AEROSOLIZED LUCINACTANT DELIVERED VIA NASAL CPAP TO IMPROVE OR PREVENT BRONCHOPULMONARY DYSPLASIA IN PRETERM NEONATES 26 TO 32 WEEKS PMA WITH RDS

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Abstract Description:

Aerosolized lucinactant (AEROSURF) is a drug-device combination employing a novel delivery technology with synthetic KL4 surfactant (lucinactant). A previous study has shown that AEROSURF-treated infants 29-34 weeks PMA at higher doses (≥75 mg/kg) decreased the need for intubation, mechanical ventilation, and oxygen requirement, believed to be major risk factors in the development of BPD. Two phase 2 studies in premature infants (26-28 and 28-32 weeks PMA) requiring supplemental oxygen (FiO2 ≥0.25) received nCPAP or AEROSURF at doses of 40 to 100 mg TPL/kg. An analysis of all subjects examined the ability of AEROSURF to decrease BPD incidence and severity using 2 definitions of BPD (need for supplemental O2 at 36 weeks PMA and NIH [Jobe 2001]). In this population, AEROSURF may be able to reduce the overall incidence and severity of BPD. Further study is warranted.

AEROSOLIZED LUCINACTANT DELIVERED VIA NASAL CPAP TO IMPROVE OR PREVENT BRONCHOPULMONARY DYSPLASIA IN PRETERM NEONATES 26 TO 32 WEEKS PMA WITH RDS

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ABSTRACT

Introduction: Nasal CPAP (nCPAP) is commonly used in preterm infants for respiratory support, but this precludes early surfactant delivery. Aerosolized lucinactant (AEROSURF) is a drug-device combination employing a novel delivery technology with lucinactant, a synthetic surfactant. A previous study has shown that AEROSURF-treated infants 29-34 weeks PMA at doses ≥ 75 mg TPL/kg decreased the need for intubation, mechanical ventilation, and supplemental oxygen, all major risk factors for the development of BPD.
Methods: In two phase 2 studies, premature infants (26-28 and 28-32 weeks post-menstrual age [PMA]) requiring $FiO_2 \geq 0.25$ received nCPAP or AEROSURF at doses of 40-100 mg/kg. Analysis of all subjects examined whether AEROSURF decreases BPD incidence and severity using 2 definitions (supplemental O_2 at 36 weeks PMA and NIH [Jobe 2001]).
Results: 48 (26-28 weeks PMA) and 213 (28-32 weeks PMA) subjects were enrolled into these two studies. The incidence of BPD in AEROSURF-treated infants was significantly less at 26-28 weeks PMA. At doses ≥ 75 mg TPL/kg, BPD incidence and severity are decreased.
Conclusion: In this population, AEROSURF may be able to reduce the incidence and severity of BPD. Further study is warranted.

BACKGROUND

Nasal continuous airway pressure (nCPAP) is commonly used in preterm infants for respiratory support, but this precludes early surfactant delivery. Aerosolized lucinactant (AEROSURF) is a drug-device combination employing a novel delivery technology with lucinactant, a synthetic surfactant. A previous study (Protocol 03-CL-1201; NCT02074059) has shown that AEROSURF-treated infants up to 34 weeks PMA at doses ≥ 75 mg total phospholipids (TPL)/kg decreased the need for intubation, mechanical ventilation, and supplemental oxygen, all major risk factors for the development of BPD. This study was excluded from the BPD analysis given the low rate of BPD in neonates of this gestational age range. However, an analysis of all 3 phase 2 studies showed a reduction in nCPAP failure rates when subjects were dosed as intended (Figure 1). It was hypothesized that AEROSURF would be able to reduce the incidence and severity of BPD in the most vulnerable population.

ACKNOWLEDGMENTS

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OBJECTIVE

The objective of this analysis was to evaluate aerosolized lucinactant in a larger population (n≈260) in a follow-on assessment from two phase 2 studies in preterm infants on nCPAP to establish safety and estimate of effectiveness of the drug-device combination product in delaying and/or preventing nCPAP failure, and reducing the incidence of severe RDS and BPD. Outcomes focused on safety (serious adverse events and adverse device events) and efficacy; the latter to be assessed primarily by the incidence of respiratory failure (intubation). Secondary efficacy measures included improvements in oxygenation and reduction in need for ventilatory support (to be assessed at 48 hours, 7 and 28 days after birth), as well as the incidence of BPD at 36 weeks PMA.

METHODS

- Two phase 2 studies (Protocols 03-CL-1401 and 03-CL-1202; NCT02528318 and NCT02636868) that enrolled 261 preterm infants 28-32 weeks PMA (166 active, 95 control), who have not been previously intubated, with RDS requiring supplemental oxygen ($FiO_2 \geq 0.25$).
- Infants received nCPAP alone or AEROSURF with nCPAP at doses of 40 to 100 mg TPL/kg.
- Analysis of all enrolled infants examined whether AEROSURF decreased BPD incidence (defined as supplemental O_2 at 36 weeks PMA; Table 2).
- Analysis of infants from both studies who received doses of ≥ 75 mg TPL/kg were examined as to whether AEROSURF decreased BPD incidence and/or severity using NIH definition (Table 3).
- Post-hoc analysis of all phase 2 studies for subjects who received doses of ≥ 75 mg TPL/kg compared AEROSURF to nCPAP alone (Figure 1).

RESULTS

Table 1. Demographics and Baseline Characteristics (Modified Intent-to-Treat)‡

Parameter		26-28 Weeks PMA		28-32 Weeks PMA	
		AEROSURF (N=24)	Control (N=24)	AEROSURF (N=142)	Control (N=71)
Gestational Age (weeks)	Mean (SD)	27.3 (0.84)	27.5 (0.76)	30.7 (1.20)	30.7 (1.17)
Sex	F/M	13/11	8/16	66/76	37/35
Race	White	12 (50%)	20 (83%)	122 (86%)	58 (81%)
Antenatal Steroids	n (%)	24 (100%)	21 (88%)	131 (92%)	70 (97%)
Multiple Births	n (%)	8 (33%)	5 (21%)	50 (35%)	22 (31%)
Cesarean section	n (%)	21 (88%)	17 (71%)	115 (81%)	56 (78%)

‡ Modified Intent-to-Treat includes all enrolled infants that received any study treatment.

Figure 1. Pooled Analysis (Post Hoc) of Three Phase 2 Studies nCPAP Failure Rates

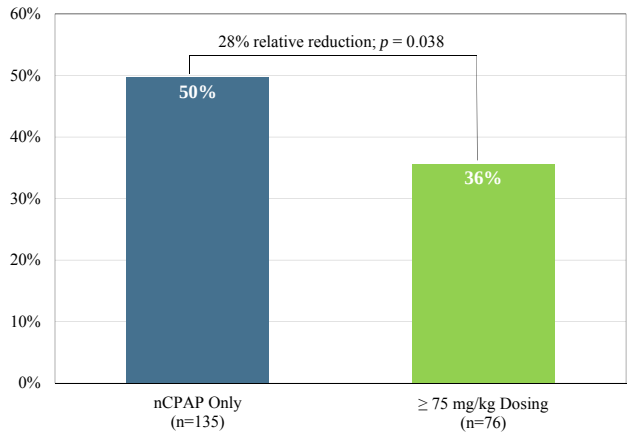

Table 2. Incidence of BPD

Definition	26-28 Weeks PMA		28-32 Weeks PMA		All Subjects#	
	AEROSURF (N=24)	Control (N=24)	AEROSURF (N=142)	Control (N=71)	AEROSURF (N=166)	Control (N=95)
O_2 at 36 Weeks	0 (0%)	6 (25%)	14 (10%)	10 (14%)	14 (8%)	16 (17%)
p-value†	0.02*		0.37		0.04*	

† Chi Square test; * p-value ≤ 0.05
# Post hoc analysis

Table 3. Severity of BPD

Definition		AEROSURF (≥75mg/kg) (N=88)	Control (N=95)	*p*-value†
O_2 at 36 Weeks	Incidence	7 (8.0%)	16 (16.8%)	0.07
NIH definition	Mild	3 (3.4%)	4 (4.2%)	0.12
	Moderate	3 (3.4%)	4 (4.2%)	
	Severe	1 (1.1%)	8 (8.4%)	

† Chi Square test; * p-value ≤ 0.05

Definitions of BPD:
- BPD incidence is the number of infants receiving supplemental oxygen at 36 weeks PMA.
- Severity of BPD is based on NIH definition (Jobe and Bancalari, 2001). In addition to supplemental oxygen >21% for at least 28 days, at 36 weeks PMA or discharge, mild severity is breathing room air or 22%, moderate is >22% to <30% oxygen, and severe is ≥ 30% oxygen and/or positive pressure.

CONCLUSIONS

- In this population, AEROSURF may reduce the incidence and severity of BPD.
- Decreases in the incidence of BPD was seen for both trials, with a *p*-value of 0.02 for the results for infants 26-28 weeks PMA, and 0.04 for all subjects (post hoc).
- A decrease in the incidence and severity of BPD in infants receiving ≥ 75 mg TPL/kg of AEROSURF (both trials combined).
- This may be mediated/achieved by reducing the need for invasive respiratory support or via anti-inflammatory properties of KL4 surfactant.
- Further evaluation of the drug-device combination therapy is warranted.