A MULTINATIONAL, MULTICENTER, MASKED, RANDOMIZED, PARALLEL GROUP, CONTROLLED STUDY TO ASSESS THE SAFETY AND EFFICACY OF LUCINACTANT FOR INHALATION VERSUS NCPAP ALONE IN PRETERM NEONATES 26 TO 32 WEEKS GESTATIONAL AGE WITH RESPIRATORY DISTRESS SYNDROME

Protocol No.:	03-CL-1702
Study Phase:	2b
Investigational Product:	AEROSURF® (lucinactant for inhalation)
IND Number:	119438
ClinicalTrials.gov No.:	TBD
EudraCT No.:	2018-000106-32

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A Multinational, Multicenter, Masked, Randomized, Parallel Group, Controlled Study to Assess the Safety and Efficacy of Lucinactant for Inhalation versus nCPAP Alone in Preterm Neonates 26 to 32 Weeks Gestational Age with Respiratory Distress Syndrome

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1 LUCINACTANT FOR INHALATION PROTOCOL 03-CL-1702

1.1 Summary

Protocol Number	03-CL-1702
Title:	A Multinational, Multicenter, Masked, Randomized, Parallel Group, Controlled Study to Assess the Safety and Efficacy of Lucinactant for Inhalation versus nCPAP alone in Preterm Neonates 26 to 32 Weeks Gestational Age with Respiratory Distress Syndrome
Phase:	2b
US IND Number:	119438
ClinicalTrials.gov No.	TBD
EudraCT No.	2018-000106-32
Sponsor:	Windtree Therapeutics, Inc. (Windtree), Warrington, PA, USA
Committees:	Data Monitoring Committee (DMC)
Study Drug and Device:	Lucinactant for inhalation (AEROSURF®, an investigational, drug-device combination product) at 30 mg total phospholipids (TPL)/ml of lucinactant delivered by the AEROSURF Delivery System (ADS) utilizing a capillary-based aerosol generator (CAG).
Active Ingredients:	A 21-amino acid hydrophobic synthetic peptide (sinapultide, KL_4 peptide), combined with the phospholipids dipalmitoylphosphatidyl-choline (DPPC) and palmitoyloleoyl-phosphatidylglycerol, sodium salt (POPG, Na), and the fatty acid palmitic acid (PA).
Rationale:	Respiratory distress syndrome (RDS) of the newborn is a disease that results from insufficiency of pulmonary surfactant in the immature neonatal lung, which carries high morbidity and mortality, especially in very preterm neonates. Exogenous surfactant replacement therapy (SRT) reduces mortality and morbidity and is recommended by multiple

international guidelines. However, SRT requires endotracheal intubation to instill surfactant, often with concomitant positive pressure mechanical ventilation (MV) or insertion of an intratracheal catheter to deliver surfactant ("minimally invasive"). Intubation or insertion of an intratracheal catheter and MV have potentially deleterious effects to the infant and may lead to short- or long-term morbidities.

To avoid endotracheal intubation or intratracheal catheter insertion and MV in preterm neonates with mild to moderate RDS, the use of non-invasive respiratory support with nasal continuous positive airway pressure (nCPAP) has become a widely accepted practice, but SRT cannot be delivered with nCPAP. Although oftentimes successful, nCPAP will fail in approximately one-third to two-thirds of preterm neonates, who generally then require endotracheal intubation, MV, and, in many cases, administration of delayed SRT. Importantly, earlier SRT is more effective than delayed SRT; thus, the inability to administer SRT in conjunction with nCPAP may result in suboptimal timing for SRT to treat RDS.

Therefore, an unmet medical need exists for a means to deliver SRT to preterm neonates with RDS supported with nCPAP early in the course of the disease. This strategy has the potential to prevent progression of RDS that could lead to the development of respiratory failure, and thereby avoid the need for endotracheal intubation and MV, or reduce the duration of MV, and the resultant potential for morbidity and associated complications. The ability to administer SRT non-invasively via an aerosol while infants are on nCPAP support has the potential to address this unmet need.

Windtree Therapeutics, Inc. (Windtree) has developed lucinactant for inhalation (AEROSURF), an investigational drug-device combination product, to deliver aerosolized SRT to preterm neonates with RDS who are being supported with nCPAP. The drug component of lucinactant for inhalation is lyophilized lucinactant, a lyophilized form of SURFAXIN® (lucinactant) Intratracheal Suspension, an exogenous SRT approved by the U.S. Food and Drug Administration (NDA 021746); however, not

currently marketed based solely on business considerations (not as the result of any safety, efficacy, or quality concerns). The device component, the AEROSURF Delivery System (ADS), uses novel technology to aerosolize reconstituted lucinactant .

Three studies of lucinactant for inhalation have been conducted: in preterm neonates 29 to 34 weeks PMA in an open-label safety study (Protocol 03-CL-1201) at escalating theoretical doses of 25, 50, 75, 100 and 150 mg TPL/kg (N=80); in preterm infants 26 to 28 weeks PMA in an open-label safety study (Protocol 03-CL-1401) at escalating theoretical doses of 50, 75, and 100 mg TPL/kg (N=64); and in preterm neonates 28 to 32 weeks PMA in a double-blind safety and efficacy study (Protocol 03-CL-1202) at parallel theoretical doses of 40 mg TPL/kg, 80 mg TPL/kg, and nCPAP only (N=221). In all studies, lucinactant for inhalation was generally well tolerated and there were no safety signals of concern noted with any of the doses. Complications of prematurity, including pulmonary air leak, were comparable between active treatment (lucinactant for inhalation) and control groups (nCPAP alone).

In Studies 03-CL-1201 and 03-CL-1401, exploratory assessment of clinical efficacy suggested that lucinactant for inhalation may be providing beneficial effects. In Study 03-CL-1202, assessment of clinical efficacy noted that fewer subjects in the 80 mg TPL/kg treatment group were intubated for MV or SRT, or met the criteria for respiratory failure, compared to subjects in the nCPAP only group, when lucinactant for inhalation therapy was delivered as intended.

In addition, data from previous studies suggest that a larger initial dose of lucinactant might be needed to improve and maintain pulmonary function; therefore; based on these studies, Windtree will evaluate a lucinactant for inhalation at an initial treatment dose of 160 mg TPL/kg, with up to 3 repeat treatments at 80 mg TPL/kg, versus nCPAP alone. Results from preclinical and clinical trials, including Studies 03-CL-1201, 03-CL-1401, and 03-CL-1202, support the safety and

	potential efficacy of this treatment regimen, including the total dose of lucinactant for inhalation to be delivered.
Objectives:	To evaluate the safety and efficacy of lucinactant for inhalation delivered by the next generation ADS device in conjunction with nCPAP, in comparison to nCPAP alone, in preterm neonates with RDS, as assessed by the incidence of and time to respiratory failure due to RDS in the first 72 hours and through 28 days of life, oxygen saturation and use of supplemental oxygen, all-cause mortality through 28 days of life, the incidence of bronchopulmonary dysplasia (BPD) at 36 weeks PMA, and the duration of mechanical ventilation. In addition, this study will evaluate the device performance and the ability to administer up to 3 lucinactant for inhalation repeat treatments.
Primary Endpoint:	The primary endpoint for this study is the number of subjects with respiratory failure due to RDS or death within the first 28 days of life. Respiratory failure due to RDS is defined as intubation (including intratracheal catheter placement) for MV and/or surfactant administration.
Key Secondary Endpoints:	The key secondary endpoints of this study include the evaluation of the following: • Respiratory failure through 72 hours and 28 days of life • Time to respiratory failure through 72 hours and 28 days of life • BPD and survival without BPD at 36 weeks PMA • Severity of BPD at 36 weeks PMA • Oxygen saturation and use of supplemental oxygen • All-cause mortality through 28 days of life and 36 weeks PMA

Other Secondary Endpoints	Other secondary endpoints of this study include the evaluation of the following: • Common complications of prematurity through 36 weeks PMA • Duration of MV and oxygen requirement through 36 weeks PMA • Changes in fraction of inspired oxygen (FiO_2), partial pressure of carbon dioxide (PCO_2) and oxygen (O_2) saturation, as determined by pulse oximetry (SpO_2) over the first 72 hours of life, and over the first 7 days of life for FiO_2. • Number and duration of re-hospitalizations and reason for re-hospitalization through 12 months corrected age. • Respiratory medications through 12 months corrected age.
Study Design:	This study is a multinational, multicenter, double-blind (masked), parallel group, randomized, controlled study to evaluate the safety and efficacy of lucinactant for inhalation in conjunction with nCPAP compared with nCPAP alone, in preterm neonates 26 to 32 completed weeks PMA who are being cared for in a neonatal intensive care unit (NICU), who had successful implementation of non-invasive respiratory support or ventilation within 30 minutes of birth, and who are candidates for SRT. It is strongly recommended that the initial mode of support is study nCPAP (bubble nCPAP); however, other non-invasive modes are acceptable if the investigator feels it is safe to switch the subject to study nCPAP following consent and screening. There will be 2 phases in the study, a primary phase through 36 weeks PMA or 28 days of life (whichever is longer), and a longer-term follow-up phase through 12 months corrected age. Data will be analyzed and reported at the completion of each respective study phase. Before study enrollment, legally authorized representatives will provide a signed informed consent form (ICF) for each potential subject; it is recommended that informed consent be obtained antenatally. Qualification for study enrollment will be established after confirmation that the subject has met all of the inclusion criteria and none of the exclusion criteria. The clinical criteria for enrollment may be met prior to

informed consent being obtained; however, no study-specific procedures that are not part of the required care of the subject at the institution may be performed until the informed consent has been provided by a legally authorized representative of the subject. Time to treatment is potentially an important factor in the success of non-invasive delivery of surfactant. Because of this and other operational factors, antenatal consent should be obtained where permitted.

Inclusion criteria to be met within the first 6 hours after birth include respiratory insufficiency with a requirement for nCPAP of 5 to 7 cm H_2O and an $FiO_2 > 0.25$ to ≤ 0.35, to maintain SpO_2 of 90% to 95% for at least 15 minutes. As soon as study qualification has been confirmed and the informed consent is signed, subjects will be randomized to an active treatment group or to the control group (nCPAP only, with simulated ["sham"] study drug treatment). Study treatment (160 mg TPL/kg lucinactant for inhalation or sham/control) must be initiated as soon as possible (within 2 hours of randomization), but no more than 8 hours after birth. Neonates who are randomized and on study nCPAP but no longer meet qualification criteria before treatment will still receive the study treatment, unless it is unsafe to do so in the opinion of the investigator. In order to ensure correct functioning of the ADS and reinforce study treatment procedures, the first 2 subjects at each site will be dosed open-label on active study treatment (initial dose of 160 mg TPL/kg lucinactant for inhalation). All procedures for treatments and repeat treatments are exactly the same.

Subsequent to the initial dose of 160 mg/kg lucinactant for inhalation or sham, subjects are eligible to receive up to 3 repeat study treatments (a total of 4 study treatments) of active or sham to which they are originally assigned; however, the dose of the active treatment will be 80 mg TPL/kg. Repeat treatments will be given as soon as 20 minutes from completion of the previous treatment up to 36 hours after randomization if the subject meets repeat treatment criteria (as described in the "Treatment Groups" section). If the subject is not on room air ($FiO_2 = 0.21$) at the conclusion of any active or sham study treatment

dosing (eg, 50 minutes after treatment initiation), the subject should receive a repeat treatment as soon as possible after the end of treatment (but ≥ 20 minutes), unless to do so would present a risk to the subject in the opinion of the principal investigator (PI). Subjects randomized to the control group will be continued on nCPAP alone but will receive repeated sham treatments to maintain study masking. The PI will follow routine practice guidelines to determine when a subject in either treatment group requires escalation of respiratory support including endotracheal intubation or rescue surfactant therapy.

Subjects in the active treatment group will receive lucinactant for inhalation at a concentration of 30 mg TPL/ml, at a rate of delivery of approximately 4.2 mg TPL/L in aerosol carrier gas flow of 3 L/min. The delivered dose of 160 mg TPL/kg (80 mg TPL/kg for repeat treatments) is based on the predetermined administration time of approximately 100 minutes of aerosol delivery (50 minutes for repeat treatments). Reconstituted lucinactant will be delivered by the investigational ADS device in conjunction with a commercially available nCPAP generator and patient interface. Treatment assignments will be masked from the PI and applicable study staff, bedside care team, sponsor (as applicable), and subject's legally authorized representative.

All enrolled subjects will receive study treatment in a NICU: a specialized care center staffed by neonatologists, nurses, and respiratory therapists who are experienced in the delivery of emergent care to the preterm neonatal population. Neonates in the NICU are continuously monitored using advanced and sophisticated monitoring equipment, and there is ready and immediate access to equipment, medications, and skilled personnel that may be needed to address emergent developments. Interventions such as endotracheal intubation, MV, and surfactant administration will be readily available to all study subjects if clinically indicated in accordance with the high-level standard-of-care customary in the NICU.

Neonates will be followed for the primary phase through 36 weeks PMA (or 28 days of life, whichever is later), hospital discharge, hospital

transfer, or death (whichever occurs first). For the longer-term follow-up phase, neonates will be evaluated by phone at 6-months corrected age and a visit at 12-months corrected age. Assessments during the longer-term follow-up include number of days on respiratory support, hospitalization information, overall health assessment, an abbreviated physical examination, and an abbreviated neurologic assessment.

Study Population: The study population will be comprised of preterm neonates 26 to 32 completed weeks PMA who are spontaneously breathing and receiving care in a NICU and are receiving bubble nCPAP as the primary support modality for RDS. Enrollment will be conducted by strata: 26 to 28 completed weeks PMA and 29 to 32 completed weeks PMA. In order to evaluate strata, each stratum will enroll a minimum of 7 subjects per arm (approximately 20% of total).

The study population will be randomized in a 1:1 ratio into 1 of 2 treatment groups (see "Treatment Groups" section).

Study Sample Size: A total of up to 130 study subjects (approximately 50% in in each treatment group) will be enrolled.

Number of Sites: Approximately 20 study sites in North America, Europe, Asia, and/or Latin America.

Study Duration: Overall, study enrollment will be completed in approximately 8 to 9 months, with the last subject reaching 36 weeks PMA approximately 10 months from the time the first subject enrolled.

For the primary phase of the study, subject participation will be from ≤ 6 hours following birth until 36 weeks PMA (or 28 days of life, whichever is later), hospital discharge or transfer, or death, whichever occurs first. Follow-up through 12-months corrected age will be done for the secondary phase of the study.

Method of Administration:

Subjects randomized to the active treatment groups will be administered an investigational drug-device combination product, lucinactant for inhalation, in conjunction with nCPAP. Reconstituted lyophilized lucinactant (reconstituted with sterile water for injection) will be aerosolized by the investigational ADS device and introduced into the nCPAP circuit. Those randomized to the control (nCPAP only) group will receive nCPAP alone. In order to maintain treatment masking, "sham" study treatment will be used: the ADS will be brought to the bedside, appropriate visual shielding will be employed, but the ADS will not be used and no study drug will be administered.

The theoretical inhaled dose (in mg TPL/kg) can be controlled based on the duration of exposure to the aerosol. This inhaled dose is a function of the concentration of lucinactant in the aerosol, the amount of aerosol inhaled by the subject (estimated by the subject's minute ventilation, assuming that all gas inhaled by the subject contains the same concentration of aerosol), and the duration of exposure to the aerosol.

Treatment Groups:

160 mg/kg 160 mg TPL/kg of lucinactant for inhalation, delivered as two consecutive 50-minute administrations, in conjunction with nCPAP (N ≈ 65).

Up to 3 repeat study treatments of 80 mg TPL/kg administered over 50 minutes will be given if repeat treatment criteria are met.

Control Continuous nCPAP (N ≈ 65) as sham study treatment for 110 minutes.

Up to 3 repeat sham study treatments (50 minutes) will be given if repeat treatment criteria are met.

The first 2 subjects at each site will be dosed open-label with active study treatment. Both open-label and masked subjects randomized to lucinactant for inhalation will be dosed with the same dosing regime (initial dose of 160 mg TPL/kg followed by 80 mg TPL/kg for repeat treatments).

Repeat treatments (active or sham) will be given ≥ 20 minutes from completion of the previous treatment up to 36 hours after randomization if subjects have a need for FiO_2 above room air (ie, $FiO_2 > 0.21$), unless it is unsafe to do so in the judgment of the PI. Masking procedures for the initial study treatment will be followed for repeat treatments, including controls.

Inclusion Criteria: Each subject must meet all inclusion criteria to be enrolled in this study:

1. Signed ICF from legally authorized representative. It is recommended that consent is obtained antenatally (where permitted).
2. Gestational age: $26^{0/7}$ to $32^{6/7}$ weeks PMA.
3. Successful implementation of non-invasive ventilation within 30 minutes after birth.
4. Spontaneous breathing.
5. Investigator determination of RDS. A chest x-ray must be obtained before treatment to confirm the diagnosis.
6. Within the first 6 hours after birth, requires an nCPAP of 5 to 7 cm H_2O that is clinically indicated for at least 15 minutes with an FiO_2 > 0.25 to ≤ 0.35 to maintain SpO_2 of 90% to 95%. Transient (<5 minutes) FiO_2 excursions outside this range do not reset the time requirement.

Exclusion Criteria: Subjects meeting any exclusion criteria must not be enrolled in this study:

1. A heart rate that cannot be stabilized above 100 beats per minute (bpm) within 5 minutes of birth.
2. Recurrent episodes of apnea requiring positive pressure ventilation (PPV) administered manually or mechanically through any patient interface.
3. A 5-minute Apgar score < 5.
4. Major congenital malformation(s) or craniofacial abnormalities that preclude the use of nCPAP, diagnosed antenatally or immediately after birth.
5. Clinically significant diseases or conditions other than RDS which could potentially interfere with cardiopulmonary function (eg, congenital heart disease, hydrops fetalis or congenital infection).
6. A known or suspected chromosomal abnormality or syndrome.
7. Premature rupture of membranes > 3 weeks.

8. Hemodynamic instability requiring vasopressors or steroids for hemodynamic support and/or presumed clinical sepsis.
9. A need for intubation and/or invasive mechanical ventilation at any time before enrollment into the study.
10. The administration (or plan for administration) of any the following:
    a) Another investigational agent or investigational medical device
    b) Any other surfactant agent
    c) Systemic corticosteroids (other than antenatal steroids)
11. Presence of air leak (pneumothorax, pneumomediastinum, pneumopericardium, subcutaneous emphysema, or definite evidence of pulmonary interstitial emphysema [PIE]) on the baseline chest radiograph or diagnosed via ultrasound or illumination.

Concomitant Medications:

All concomitant medications administered to the subject from birth until 36 weeks PMA, hospital discharge, hospital transfer, or death (whichever occurs first) will be recorded in the electronic case report form (eCRF).

Medications required for the general care of the subject are permitted with the exception of investigational agents, investigational medical devices, or any SRT before randomization. Commercially available SRTs, following study treatment, may be administered as medically indicated (ie, "rescue surfactant"). Study subjects who receive any commercial SRT while on-study will be considered treatment failures but will continue to be followed until study completion. Postnatal steroids are not permitted unless clear medical need is determined. Use of caffeine citrate or other methylxanthines is recommended.

Safety and Tolerability Endpoints:

The safety and tolerability endpoints will be assessed during the primary phase through 36 weeks PMA, hospital discharge, hospital transfer, or death, whichever occurs first, as described below.

1. All-cause mortality through 28 days of life and 36 weeks PMA
2. AEs, including adverse device effects (ADEs). SAEs that are ongoing at 36 weeks PMA will be followed for an additional 30 days
3. Concomitant medications

4. Use of any type of respiratory support (invasive or non-invasive), including an oxygen requirement ($FiO_2 > 0.21$) or the need for endotracheal intubation and MV
5. Complications of prematurity, including air leak
6. Physical examinations
7. Assessments of the following:
   a. Vital signs
   b. FiO_2
   c. SpO_2
   d. CPAP/PEEP
   e. Chest radiography prior to intubation

Early Discontinuation of Treatment:

The administration of study treatment may be discontinued at any time prior to the completion of dosing if certain device malfunctions or interruptions occur which cannot be corrected in a safe and timely manner or based on the clinical judgment of the PI. Reasons for discontinuation of study treatment include, but are not limited to the following:

1. A device malfunction occurs
2. The device shuts down as a result of a detected out of range condition
3. An AE or ADE which places subject at risk occurs (eg, pulmonary hemorrhage; airway obstruction)
4. If, in the PI's best medical judgment, initiating or continuing the subject's exposure to study treatment is not in the best interest of the subject's safety
5. Signs of acute respiratory deterioration develop, as evidenced by a clinically significant increase in respiratory rate or effort (work of breathing) plus at least one of the following:
   a) A persistent (at least 10 minutes) $FiO_2 \geq 0.70$ or sustained increase from baseline by ≥ 0.30 to maintain SpO_2 90% to 95%
   b) A persistent (at least 5 minutes) transcutaneous $PCO_2 > 70$ mmHg or an increase from baseline by ≥ 20 mmHg
   c) Recurring episodes of bradycardia
   d) A sustained apneic event (≥ 20 seconds)

Subjects whose treatment is discontinued based on the PI's judgment will continue in the study. Subjects whose treatment is discontinued based on the parent/guardian's withdrawal of consent will be withdrawn from the study and no further data collection will be done.

Statistical Analysis	The statistical analysis of objectives will be based on all enrolled preterm neonates. The subjects enrolled open-label with active treatment (the first 2 subjects from each site) will be summarized separately; however, AEs and other safety information may also be pooled with data from the double-blind portion of the study. For the efficacy analysis, populations of all randomized subjects who received any treatment (modified intent-to-treat [mITT]) and subjects with no major protocol deviations or treatment interruptions (per-protocol) will be evaluated, based upon the treatment group to which they were randomized. For the safety analysis, all subjects randomized to the control group or who received any lucinactant for inhalation (including partial doses) will be evaluated, based upon the treatment they actually received. The primary efficacy analysis will be performed using logistic regression. Secondary and tertiary endpoints will be assessed using either Cochran-Mantel-Haenszel or log-rank tests.
Interim Analyses:	During the primary phase, the chair of the data monitoring committee (DMC) will receive regular reports (eg, bi-weekly) on SAEs and AEs of interest. There will be one planned meeting when enrollment is approximately 1/3 of total; ad hoc meetings of the DMC will occur if deemed necessary to address safety in the study.

1.2 Schedule of Activities (SOA)

Measurement/Procedure	Primary Phase Through 36 Weeks PMA				Post-36 Weeks Visit	Follow-Up Period (≤ 12 Months Corr. Age)
	Screening	Primary Period (Days 1-3)	Extended Period (Days 4-7)	Final Period (Day 8 to Final Visit[1])		
Informed Consent	X					
Inclusion/Exclusion Criteria	X					
Demographics	X					
Maternal/Birth/Medical Hx	X					
Chest Radiograph[2]	X	X	X			
Respiratory support	X	X	X	X		X
Physical Examination	X			X		
Randomization		X				
Study Treatment Admin.		X				
Technical Perform. of Device		X				
PCO_2		X[3,4]				
FiO_2, SpO_2, Vital Signs, PEEP		X[3,4]	X[5]			
Respiratory ventilation/support				X	X	X
AEs and ADEs		X	X	X		
Concomitant Medication		X	X	X	X[6]	X[6]
Complications of Prematurity				X		
Final Visit/Discharge				X	X[7]	
Hosp. and Emerg. Visits Info.					X	X
Health Assessment						X
Abbrev. PE, Neuro. Exam						X[8]
Growth Assessment						X[8]

Note: Day 1 for all subjects is the day of the initial study treatment.

[1] 36 weeks PMA, hospital transfer, or hospital discharge (whichever occurs first). Subjects must remain in the study until 28 days of life, unless transferred/discharged or death.

[2] A chest radiograph must be obtained prior to dosing to confirm RDS diagnosis and absence of air leak. An additional chest radiograph is required prior to any intubation if such a procedure does not delay or compromise the emergent care of the subject.

[3] Documented at randomization, every 30 minutes after randomization until initiation of study treatment.

[4] Study Days 1-3: time 0 (study treatment initiation), 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150 minutes (± 3 minutes) after initiation (through 70 minutes for repeat treatments); 3 ± 0.5, 6 ± 1, 9 ± 1, 12 ± 1, 18 ± 2, 24 ± 2, 36 ± 2, 48 ± 2, 60 ± 2 and 72 ± 2 hours after initiation.

[5] Recorded at 08:00 and 20:00 daily through Day 7.

[6] Bronchodilators, steroids, and palivizumab (Synagis) use only.

[7] If discharge occurs after 36 weeks PMA.

[8] 12-months corrected age only.

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LIST OF ABBREVIATIONS

Abbreviation	Description
ADE	Adverse device effect
ADS	AEROSURF Delivery System
AE/TEAE	Adverse event/treatment-emergent adverse event
BPD	Bronchopulmonary dysplasia
CAG	Capillary-based aerosol generator
CFR	Code of Federal Regulations
CLD	Chronic lung disease
CPAP/nCPAP	Continuous positive airway pressure/nasal CPAP
CRF/eCRF	Case report form/electronic CRF
DMC	Data Monitoring Committee
DPPC	Dipalmitoyl phosphatidylcholine
FDA	Food and Drug Administration
FiO_2	Fraction of inspired oxygen
GA	Gestational age
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act of 1996
ICF	Informed consent form
ICH	International Conference on Harmonisation
IEC/IRB	Independent Ethics Committee/Institutional Review Board
IND	Investigational new drug
IPP	Intermittent positive pressure
ITT	Intent-to-Treat
IVH	Intraventricular hemorrhage
IRT	Interactive response technology
KL_4	21-amino acid hydrophobic synthetic peptide, also known as sinapultide
MMAD	Mass median aerodynamic diameter
MV	Mechanical ventilation
NDA	New drug application

Abbreviation	Description
NEC	Necrotizing enterocolitis
NICU	Neonatal intensive care unit
NOAEL	No observed adverse effect level
PA	Palmitic acid
PCO_2	Partial pressure of carbon dioxide
PDA	Patent ductus arteriosus
PI	Principal Investigator
PIE	Pulmonary interstitial emphysema
PMA	Post-menstrual age
POPG, Na	Palmitoyloleoyl-phosphatidylglycerol, sodium salt
PVL	Periventricular leukomalacia
RDS	Respiratory distress syndrome
ROP	Retinopathy of prematurity
SAE	Serious adverse event
SIV	Site initiation visit
SpO_2	Oxygen saturation measured by pulse oximetry
SRT	Surfactant replacement therapy
TPL	Total phospholipids
UADE	Unanticipated adverse device effect
US	United States
Vm	Minute ventilation
WMA	World Medical Assembly

2 INTRODUCTION

The purpose of this study is to evaluate the safety and efficacy of lucinactant for inhalation used in conjunction with nasal continuous airway pressure (nCPAP), in comparison with nCPAP alone, in preterm neonates 26 to 32 completed weeks postmenstrual age (PMA) with respiratory distress syndrome (RDS) of the newborn.

Aerosolized surfactant delivery potentially addresses an unmet medical need by providing a means to deliver surfactant to preterm neonates with RDS who are treated non-invasively with nCPAP, thereby providing surfactant replacement therapy (SRT) early in the disease course while avoiding the complications associated with endotracheal intubation and mechanical ventilation inherent in conventional surfactant delivery.

This clinical study is for preterm neonates 26 to 32 completed weeks PMA and is designed to assess the safety and efficacy of a novel SRT, lucinactant for inhalation, administered at an initial dose of 160 mg total phospholipids (TPL)/kg, and subsequent retreatments at a dose of 80 mg TPL/kg. A preceding dose-escalation safety study, Protocol 03-CL-1201, was conducted in preterm neonates 29 to 34 completed weeks PMA, whose intent was to establish that lucinactant for inhalation is generally well tolerated in dosages of 25, 50, 75, 100 and 150 mg TPL/kg. A similar dose-escalation safety study (Protocol 03-CL-1401) in preterm infants 26 to 28 weeks PMA was conducted to establish that lucinactant for inhalation is generally well tolerated in dosages of 50, 75, 100, and 150 mg TPL/kg; the 150 mg TPL/kg dose group was not done for administrative reasons. A safety and efficacy study, Protocol 03-CL-1202, completed the primary phase in July of 2017; assessment of the extended phase through 1-year corrected age is still ongoing. There have been no safety signals of concern from any of these studies.

Findings from the previous 3 studies (03-CL-1201, 03-CL-1401, 03-CL-1202) and this study will contribute to the development and design of future investigations of this novel drug/device combination product.

All study procedures and assessments are to be conducted in accordance with local and regional regulatory requirements, institutional review board (IRB)/independent ethics committee (IEC) requirements, International Conference on Harmonisation Good Clinical Practices (ICH GCP) Guidelines, and local institutional practices.

Definitions of study terms are provided in Appendix 1 - Protocol Definitions.

2.1 Treatment of Neonatal Respiratory Distress Syndrome

RDS of the newborn is a disease that results from insufficiency of pulmonary surfactant in the immature neonatal lung, which occurs with high frequency in preterm infants and caries high morbidity and mortality, especially in very preterm infants. Exogenous surfactant treatment reduces mortality and morbidity in preterm infants with RDS (1,2). Intratracheal SRT has well-established benefits in infants with RDS and has become a standard, recommended therapy for this condition (3,4,5,6). Early SRT is more effective in reducing morbidity and mortality due to RDS than SRT delivered later (2), and multiple doses are sometimes necessary (1).

Intratracheal instillation of surfactant into the lung requires endotracheal intubation or insertion of a thin intratracheal catheter, often with concomitant positive pressure mechanical ventilation (MV). However, endotracheal intubation is an invasive, painful procedure that itself has potential deleterious effects to the infant, including hypoxemia, bradycardia, hypertension, increases in intracranial pressure and cerebral blood flow which may increase the risk of intraventricular hemorrhage (IVH) (7,8), and tracheal injury which may lead to the development of subglottic stenosis (9). Further, MV is associated with morbidities such as ventilator-associated lung injury and volutrauma/barotrauma resulting in air leak syndromes such as pneumothorax and/or pulmonary interstitial emphysema (PIE). MV may also contribute to development of chronic lung disease (CLD)/bronchopulmonary dysplasia (BPD) (10).

2.1.1 Continuous Positive Airway Pressure in Neonatal Respiratory Distress Syndrome

In order to avoid endotracheal intubation and MV in preterm neonates with mild-to-moderate RDS, a strategy of using nCPAP as an effective means of providing ventilatory support is now accepted and recommended practice (3,4,5,6,11). nCPAP improves respiratory function in neonates by increasing functional residual capacity, improving lung compliance and dilating upper airway structures, thereby improving gas exchange and reducing work of breathing (11,12).

Devices that generate and deliver nCPAP, as well as patient interfaces such as nasal prongs, have been specifically designed, manufactured, and made commercially available for use in neonates. Devices to generate nCPAP include those with continuous humidified flow (eg, bubble CPAP) and more complex devices with variable flow (eg, a mechanical ventilator set to CPAP mode). Because neonates are obligate nose breathers, several patient interface devices exist that can be used to deliver CPAP via the nose such as nasal masks, short bi-nasal prongs, and nasopharyngeal tubes.

Studies in very preterm neonates of initial treatment of RDS with nCPAP alone (13,14,15,16), including meta-analyses (17,18), have shown outcomes with this approach that are similar to traditional, early treatment with intratracheal surfactant. These studies have consistently shown that in neonates treated with nCPAP, the need for surfactant therapy is less than that of neonates treated with intubation and SRT, and that the important outcome of death or bronchopulmonary dysplasia (BPD, defined as the need for oxygen [O_2] treatment at 36 weeks PMA) is equal or less frequent with nCPAP. In neonates treated with nCPAP, approximately 33-67% of patients required intubation and intratracheal surfactant replacement, meaning that ⅓ to ⅔ of patients were able to avoid intubation altogether. Thus, the strategy of initially supporting neonates with nCPAP and reserving SRT only for those who require intubation appears to be reasonably effective and potentially safer by avoiding intubation. Two meta-analyses (10,19) and a systematic review (20) have suggested that use of nCPAP as the primary respiratory support modality in preterm neonates reduces the need for intubation and the rate of BPD, with a number need to treat (NNT) of 25 for BPD (10).

In neonates 24-28 weeks gestation, the rate of air leak (pneumothorax, pneumomediastinum or pulmonary interstitial emphysema) was generally low (3 to 9.6%), but in some reports were greater in the nCPAP groups compared to the intubation groups (12,13,14). Air leaks have been reported in as many as 21% of neonates in this gestational age range treated with a restrictive intubation strategy using nCPAP (21).

Older gestational age infants treated with nCPAP may be at higher risk of air leak than younger infants (22). In a cohort of 297 neonates 25-32 weeks gestation with RDS initially treated with nCPAP alone, 65 (22%) overall required intubation ("nCPAP failure"). The rate of nCPAP failure was 45% in the subgroup 25-28 weeks' gestation, consistent with prior reports, where only 15% of infants 29-32 weeks' gestation had nCPAP failure. Notably, the rate of pneumothorax prior to intubation was 10% in the younger cohort (also consistent with most prior reports) but was 23% in the older gestational age infants as a whole and 47% in those older infants who failed nCPAP.

2.1.2 Unmet Medical Need for Aerosolized Surfactant Replacement Therapy

Several studies have demonstrated that earlier intratracheal SRT is more beneficial than SRT delivered later (2). For this reason, guidelines recommend that when SRT is used it be given as early as possible (3,4,5,6). However, when nCPAP is used as initial respiratory support, SRT is necessarily delayed in those neonates who ultimately require endotracheal intubation.

Thus, an unmet medical need exists for a means to deliver SRT to preterm neonates with RDS supported with nCPAP early in the course of the disease. This strategy has the potential to improve RDS prior to the development of respiratory failure, thereby avoiding the need for endotracheal intubation and MV and the resultant potential for morbidity and complications. The ability to administer SRT via aerosol has the potential to address this unmet need.

Efforts to aerosolize surfactants in clinical models have been largely unsuccessful to date (23) because of the limited capability of currently available aerosol generators to aerosolize surfactants in the amount needed to achieve a therapeutic benefit. Delivery of surfactant aerosol to the lungs has been limited by technical constraints of currently available aerosol generators and system configurations. Compared with surfactant administration via endotracheal instillation, surfactant administration via aerosolization is highly inefficient and dose delivery is limited (24). Newer aerosol generator technologies may allow for administration of aerosolized surfactant in sufficient quantities to achieve a therapeutic response. As with liquid surfactant, aerosolized surfactant is most likely delivered preferentially to the ventilated parts of the lungs (25). It is therefore likely that improving lung aeration by providing appropriate ventilatory support during aerosol delivery, as with nCPAP, would improve the delivery of aerosolized surfactant.

2.2 Development of Aerosolized Surfactant with Lucinactant for Inhalation

To address this unmet need, Windtree Therapeutics, Inc. (Windtree) developed lucinactant for inhalation, an investigational drug-device combination product, to deliver aerosolized SRT to preterm neonates with RDS who are being supported with nCPAP. Lucinactant for inhalation is comprised of a drug component, lyophilized lucinactant, and a device component, the AEROSURF® Delivery System (ADS). Lyophilized lucinactant is a lyophilized form of SURFAXIN® (lucinactant) Intratracheal Suspension, an exogenous SRT approved by the U.S. Food and Drug Administration (NDA 021746) (not currently marketed based solely on business considerations and not as the result of any safety, efficacy, or quality concerns). The ADS device uses novel capillary-based aerosol generator (CAG) technology to aerosolize reconstituted lucinactant, providing a high-density surfactant aerosol output with an appropriate particle size (2 to 4 microns mass median aerodynamic diameter [MMAD]) for respiration and deposition within the neonatal lung. The ADS may allow aerosolized lucinactant to be deposited in the lungs of preterm neonates in sufficient quantities to affect a therapeutic response analogous to that of endotracheal instillation of surfactant.

Nonclinical studies using the CAG technology in preterm lambs have demonstrated that aerosolized lucinactant significantly improved lung mechanics and gas exchange compared with

preterm lambs receiving CPAP alone (26). In parallel, pilot clinical studies in neonates with RDS (Study KL4-CPAP-01) (27) as well as in adults with asthma and cystic fibrosis (Study KL4-ASTH-01) have demonstrated that lucinactant aerosolized with commercially available nebulizers appears to be generally well-tolerated. The ADS represents the clinical version of the CAG technology, which is being used in clinical trials, including the current study, to aerosolize lucinactant.

2.3 Clinical Experience with Aerosolized Lucinactant

Two Windtree-sponsored clinical studies have been conducted using aerosolized lucinactant administered with standard, commercially available nebulizers (Studies KL4-CPAP-01 and KL4-ASTH-01). In addition, aerosolized lucinactant administered with the ADS has been investigated in two completed Windtree-sponsored clinical trials (Studies 03-CL-1201 and 03-CL-1401) and one Windtree-sponsored clinical trial that has completed its primary phase and assessment of the longer-term follow-up phase is ongoing (Study 03-CL-1202). These studies are briefly described below, and in greater detail in the Investigator's Brochure.

2.3.1 Preliminary Studies Using Commercially Available Nebulizers

Study KL4-CPAP-01 (27) was a Phase 2, multicenter pilot study in preterm neonates investigating the feasibility of delivering aerosolized lucinactant to preterm neonates at risk for RDS administered using the Aeroneb® Pro Nebulizer System in conjunction with nCPAP, which delivered a lucinactant output of approximately 4 µL/second. The majority (12, 70%) of the 17 neonates studied received a single treatment of study drug, with exposure dosage of approximately 72 mg TPL of aerosolized lucinactant in a volume of 43 mL over the 3-hour treatment. No device-related serious adverse events (SAEs) occurred. Adverse events during dosing (peridosing events) included oxygen desaturation (53% of patients), pallor (6%), nasal irritation (6%), skin irritation (6%), and apnea (29%); many of these are commonly observed in premature infants on nCPAP. Five subjects (30%) required subsequent endotracheal surfactant replacement, which is somewhat better than the rate reported in the literature (13,14). The study demonstrated that it is feasible to deliver aerosolized lucinactant in conjunction with nCPAP and that the treatment was generally well-tolerated by preterm neonates.

Study KL4-ASTH-01 was a Phase 1b study that assessed the safety and tolerability of aerosolized lucinactant in a placebo-controlled study of adults with mild persistent asthma. Six healthy adult volunteers and 9 adults with mild persistent asthma were administered aerosolized lucinactant by the Aeroneb® Pro Nebulizer System. In this study, $\leq$ 24.5 mg TPL was administered at

approximately 1 mg/minute. The treatment was well-tolerated with no SAEs. Pulmonary function and clinical signs and symptoms of asthma generally remained unchanged from baseline and were similar in both treatment groups.

The study demonstrated it is feasible to deliver aerosolized lucinactant to adults and that the treatment was generally well-tolerated.

2.3.2 Clinical Studies using the AEROSURF Delivery System

Lucinactant aerosolized using the prototype ADS has been studied in two completed Phase 2a study in infants: 29 to 34 weeks PMA (Study 03-CL-1201) and 26-28 weeks PMA (Study 03-CL-1401). Another study (Study 03-CL-1202) completed its primary phase and assessment of the longer-term follow-up phase is ongoing. Results of these studies are summarized below and results apropos to the selection of dosages in this study are summarized in Section 3.2.3.5.

2.3.2.1 Study 03-CL-1201

Study 03-CL-1201 was a Phase 2a, multicenter, randomized, open-label, controlled, dose-escalation study assessing the safety and tolerability of lucinactant for inhalation in preterm neonates 29 to 34 completed weeks PMA. This study was conducted at 11 study sites in the United Sates (US); neonates were enrolled at 10 centers. The primary objective was to evaluate the safety and tolerability of lucinactant for inhalation administered in escalating theoretical inhaled doses of 25, 50, 75, 100, and 150 mg TPL/kg to preterm neonates 29 weeks to 34 completed weeks PMA who were receiving nCPAP for RDS, compared to neonates receiving nCPAP alone.

A total of 80 preterm neonates were randomized; 40 received lucinactant for inhalation (8 per dose group) and 40 received standard therapy (nCPAP alone; 8 per dose group) as a control. Active and control subjects were similar in terms of gestational age, birth weight, gender, race and ethnic origin. One subject was randomized to the 100 mg TPL/kg group despite having a deteriorating clinical condition immediately prior to dosing and briefly (< 5 min) received study treatment; this subject was not included in the exploratory efficacy analyses as the subject should not have been treated. All active subjects received at least one treatment; 1 subject in the 100 mg TPL/kg group and 2 in the 150 mg TPL/kg group received 2 treatments.

Study drug treatment (initial or repeat) was discontinued early in 10 (25%) subjects: 6 (15%) due to “device failure or malfunction”; 2 (5%) due to signs of acute respiratory deterioration; and 2 (5%) due the PI’s medical judgment. “Device failure or malfunction” was selected when the ADS terminated aerosol treatment early; however, these early stoppages were due to a condition outside

of preset ranges, such as aerosol temperature. Thus, the device functioned as designed, but the full treatment was not delivered.

Safety

Primary safety and tolerability measures included AEs, air leak, complications of prematurity, survival, and early withdrawal from the study. In addition, assessments on serum electrolytes, gastric liquid volume, and defecation were performed.

The incidence of adverse events (AEs) was comparable between treatment and control groups, occurring in 39 (98%) active subjects and 37 (93%) controls. Complications of prematurity were comparable between treatment and control groups; peri-dosing events were uncommon, occurring in 7 (18%) active subjects with no increase in incidence as dosage increased. SAEs occurred in 13 (33%) of active subjects, with no increase in incidence as dosage increased, and 7 (18%) of control subjects. Two subjects died: one subject in the 150 mg TPL/kg group experienced severe cardiopulmonary deterioration of unknown cause (suspected sepsis) 9 days after study treatment, and one control subject died of acute pulmonary hemorrhage related to RDS and treatment with poractant alfa 2 days after randomization into the study; neither death was considered by the PI to be related to study treatment or procedures.

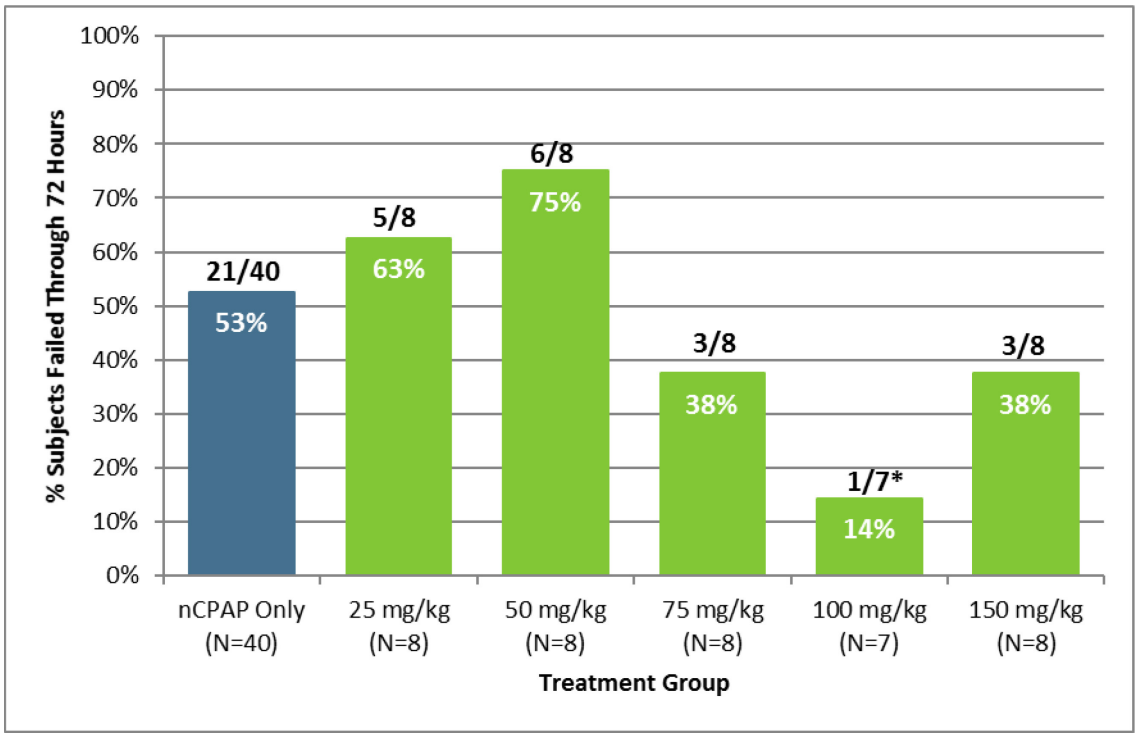
When all forms of pulmonary air leak are considered together, the incidence in active and control groups was similar. Overall, 9 (23%) active subjects experienced air leak, all of whom had pneumothorax with 2 (5%) experiencing PIE and 1 (3%) experiencing pneumomediastinum as well. The incidence across dosage groups was similar. In the control group, 7 (18%) were reported by the investigator as having air leak, 5 (13%) of whom had pneumothorax and 2 (5%) experiencing PIE. An independent review of all radiographs of all subjects confirmed the 9 air leaks in the active subjects but identified an additional 2 air leaks (both PIE) in 2 control subjects. Thus, the independent review noted a total air leak incidence of 9 (23%) among both active and control subjects.

Efficacy

The evaluation of efficacy was an exploratory endpoint in this study; no statistical testing or quantitative comparisons were performed between treatment groups or lucinactant for inhalation doses. The primary goal of this efficacy analysis was to evaluate the feasibility of measuring a variety of efficacy endpoints. Results apropos to dosage selection are presented in Section 3.2.3.

Intubation within 72 hours of life for any reason was considered a key efficacy parameter, since it generally indicates progression of RDS beyond the point where the subject can be supported on nCPAP alone and is the main intervention that lucinactant for inhalation seeks to avoid. Intubation is considered a likely candidate as the primary efficacy endpoint in future studies. Intubation occurred in 21 (53%) of control subjects (Figure 2-1). The incidence was generally similar in each of the 5 individual control groups; thus, all controls were pooled for comparison. Overall, 20 (50%) subjects in the active groups were intubated. However, notably fewer subjects were intubated with the higher 3 dosages (7/23, 30%) than with the lower 2 dosages (11/16, 69%).

Figure 2-1. Incidence of Intubation for Any Reason within 72 Hours of Life (nCPAP Failure) in Study 03-CL-1201



*One subject excluded from analysis due to being enrolled despite deteriorating clinical condition
Data source: Study 03-CL-1201 CSR, Figure 11.4-1.

There was no clear relationship between active treatment and time to intubation, likely due to the high variance of the data. However, when dosages of 75 and 100 mg TPL/kg are considered together, time to intubation appears to be delayed, supporting the use of the 80 mg TPL/kg dosage going forward.

Study 03-CL-1201 Summary

In summary, the results from this study demonstrate that delivery of reconstituted lucinactant as an aerosol using the ADS is feasible and that lucinactant for inhalation appears to be generally well-tolerated in neonates in this gestational age range with RDS, with no safety concerns identified. Exploratory assessment of clinical efficacy parameters suggests that lucinactant for inhalation increases time to intubation, and decreases the incidence of intubation in preterm neonates 29 to 34 weeks gestation PMA with RDS.

2.3.2.2 Study 03-CL-1401

Study 03-CL-1401 was a Phase 2a, multicenter, randomized, open-label, controlled dose-escalation study assessing the safety and tolerability of lucinactant for inhalation in preterm neonates 26 to 28 completed weeks PMA. The study design and objectives were substantially the same as Study 03-CL-1201 (Section 2.3.2.1), but in a lower gestational age population. Theoretical inhaled doses of 50, 75 and 100 mg TPL/kg were investigated and compared to subjects receiving standard therapy with nCPAP alone in a dose escalation manner. One repeat treatment was possible for all dosages (with a 2-hour minimum interval between treatments).

A total of 22 study sites from the US, Canada, Poland and Chile participated in the study. A total of 48 subjects were enrolled, with 8 each in the 50, 75 and 100 mg TPL/kg groups, and 24 in the control group. The study was terminated prior to subject enrollment for Dosing Group IV for administrative reasons (including resource limitations and the intent to study the 26-28 GA weeks PMA patients in an amendment to Study 03-CL-1202).

Active and control subjects were generally similar with respect to gestational age, birth weight, gender, race and ethnic origin. All active subjects received at least one treatment, and 16 (67%) received a repeat treatment.

Safety

Primary safety and tolerability measures included AEs, air leak, complications of prematurity, survival, and early withdrawal from the study.

All subjects experienced at least 1 TEAE. The most common TEAEs were neonatal apnea, neonatal anemia, neonatal jaundice, constipation, and neonatal RDS. There were 2 adverse device effects (ADEs) reported in this study: 1 subject in the 50 mg TPL/kg group experienced nasal

inflammation considered unrelated to study treatment, and 1 subject in the 100 mg TPL/kg experienced oxygen desaturation considered related to study treatment. Both events were considered mild.

Two deaths occurred during the course of the study. One subject in the 50 mg TPL/kg group experienced severe necrotizing enterocolitis (NEC) and died abruptly at approximately 6 weeks of life. One subject in the 75 mg TPL/kg group experienced pneumoperitoneum approximately 5 days after study treatment and died approximately 10 days after study treatment. Neither death was related to study treatment.

Air leaks, an AE of special interest, demonstrated a similar incidence in active and control groups. Overall, 5 (21%) active subjects experienced an air leak, of whom 2 had pneumothorax and 4 had PIE. In the nCPAP only group, the investigator reported 4 (17%) subjects as having an air leak: 3 (13%) each with pneumothorax and PIE.

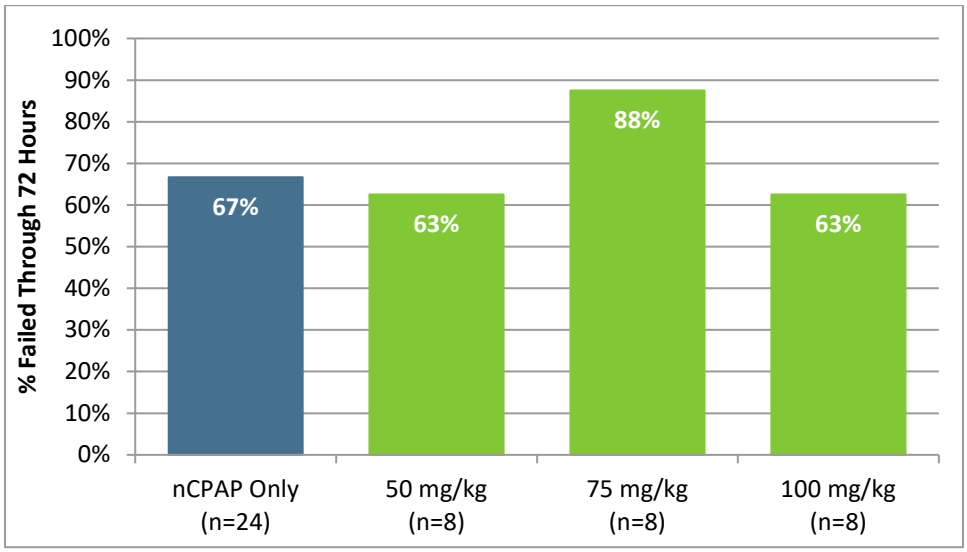
There are no clinically important differences between results for subjects who received the active treatment compared to results for subjects who received control for complications of prematurity.

Efficacy

The evaluation of efficacy was an exploratory endpoint in this study; no statistical testing or quantitative comparisons were performed between treatment groups or lucinactant for inhalation doses. As with Study 03-CL-1201, all controls were pooled for comparison.

Overall, there was no difference in the rate of nCPAP failure (intubation for MV and/or SRT) within 72 hours between any active treatment group and the control group. nCPAP failure occurred in 17 (71%) of active subjects and 16 (67%) of control subjects (Figure 2-2).

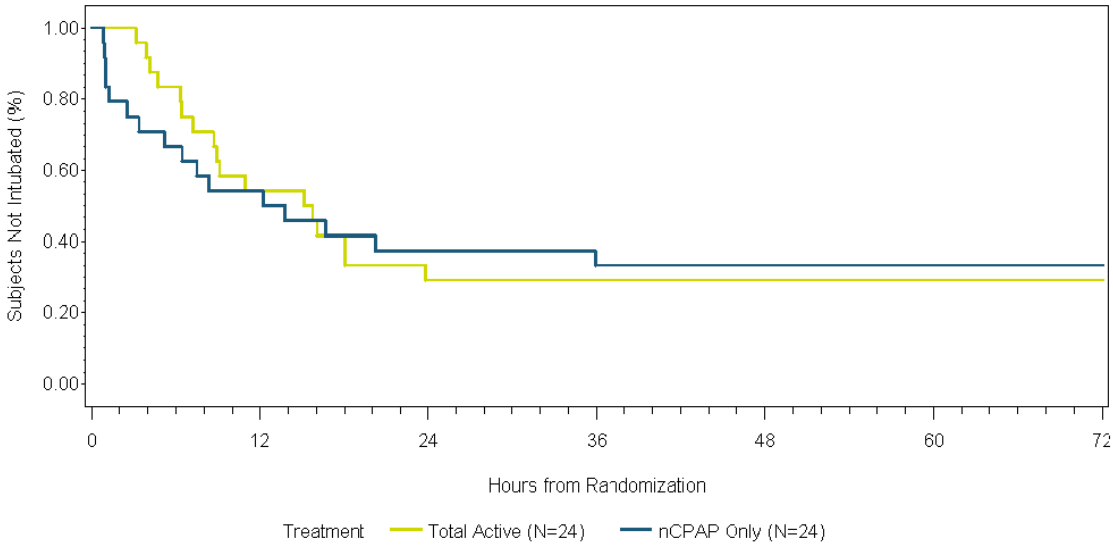
Figure 2-2. nCPAP Failure through 72 Hours from Randomization in Study 03-CL-1401.



Data source: Study 03-CL-1401 CSR, Summary Figure 1.3.1.

As in Study 03-CL-1201, there is no clear relationship between active treatment and time to intubation when all subjects are considered, likely due to the high variability of the data. However, comparing treatment groups by Kaplan-Meier graph (Figure 2-3) demonstrates that while the number of intubations was similar, intubations in the active group occurred later than intubations in the nCPAP Only group.

Figure 2-3. Time to Intubation from Randomization in Study 03-CL-1401 Intent-to-Treat Population



Data source: Study 03-CL-1401 CSR, Summary Figure 1.1.

Treatment groups in Study 03-CL-1401 were affected by unanticipated treatment interruptions, particularly the 75 mg TPL/kg group. Since treatment interruptions tended to occur more often with longer treatment times, interruptions occurred more often in the 75 mg TPL/kg group, which required a single 45 min administration for treatment, than in the 50 and 100 mg TPL/kg groups, which required 1 or 2 30-min administrations for treatment.

For incidence of BPD or incidence of survival survived without BPD, no subjects in the active groups and 6 subjects in the nCPAP only group developed BPD during the study. An exploratory comparison between the active and control groups was significant at *p*-value = 0.022 from Fisher's Exact Test. The incidence of survival without BPD was 22 (92%) and 18 (75%) subjects for the active and nCPAP only groups, respectively.

Exploratory assessment of clinical efficacy parameters, while small and potentially confounded by treatment interruptions, suggests that there was no qualitative evidence on rate of intubation; however, there was some evidence of effect in time to intubation, BPD, and fraction of inspired oxygen (FiO_2) requirements. The magnitude of the effect has not been determined and the study was not powered for comparisons between treatment groups.

2.3.2.3 Study 03-CL-1202

Study 03-CL-1202 is an ongoing Phase 2b, multinational, multicenter, masked, randomized, controlled study to evaluate the safety and efficacy of 2 different dosages of lucinactant for inhalation (40 mg TPL/kg and 80 mg TPL/kg) in conjunction with nCPAP compared with nCPAP alone (with sham study drug treatment to maintain masking), in preterm neonates 28 to 32 completed weeks PMA. Up to 2 repeat treatments of the treatment to which they are assigned were possible for all subjects if they met repeat treatment criteria. The primary endpoint for this study is to the incidence of respiratory failure or death due to RDS within the first 72 hours of life. Secondary endpoints of this study include the time to respiratory failure or death due to RDS, the incidence of BPD at 36 weeks PMA, all-cause mortality, survival without BPD at 36 weeks PMA, and incidence of pulmonary air leak; tertiary endpoints of this study include the incidence rates of common complications of prematurity and the change from baseline in FiO_2 and/or transcutaneous partial pressure of carbon dioxide (PCO_2) over the first 72 hours of life. Follow-up through 1-year corrected age constitutes the secondary phase of the study.

This study was initiated on 28 December 2015 and is being conducted in 50 study sites in North America, Europe, and South America. A total of 47 sites enrolled at least one subject when enrollment was concluded at the end of May 2017. As of the date of this protocol, enrollment, study treatment and assessment of the primary outcome have been completed; assessment of long-term follow-up results through 1-year corrected age is ongoing.

A total of 221 patients were randomized into the study. 213 patients (n=70 at 40 mg/kg, n=72 at 80 mg/kg, n=71 for the control group of nCPAP alone) received study drug or sham treatment and constitute the modified intention to treat (mITT) population and the safety population. Subjects in each group were similar in terms of GA, birth weight, gender, race and ethnic origin.

Subjects were allowed up to 2 repeat treatments. Repeat treatments were administered to 64% and 54% of the 40 and 80 mg TPL/kg dose groups respectively, compared to 63% for the nCPAP control group (sham repeat treatments). The average number of treatments for the 40 and 80 mg TPL/kg groups were 2.0 and 1.8, respectively.

Safety

Primary safety and tolerability measures include survival, AEs/ADEs, use of respiratory support including intubation, complications of prematurity, and air leak.

Most subjects (94% and 93% for the active and control groups, respectively) experienced at least one AE. A total of 50 subjects reported 28 SAEs, and a total of 22 subjects reported 10 ADEs. Overall, the incidence of air leak was lower than in prior clinical trials, and air leak incidence was lower in the 80 mg/kg group than in the 40 mg/kg group.

There are no clinically important differences between results for complications of prematurity for subjects who received the active treatment compared to results for subjects who received control.

Unanticipated interruptions in treatment administration occurred in all studies. The majority of the interruptions in this study were "syringe pressure out of range" (also known as "syringe back-pressure") due to clogging of a filter within the path of liquid reconstituted lucinactant and causing increased pressure within the ADS. No increased pressure was transmitted to the subjects.

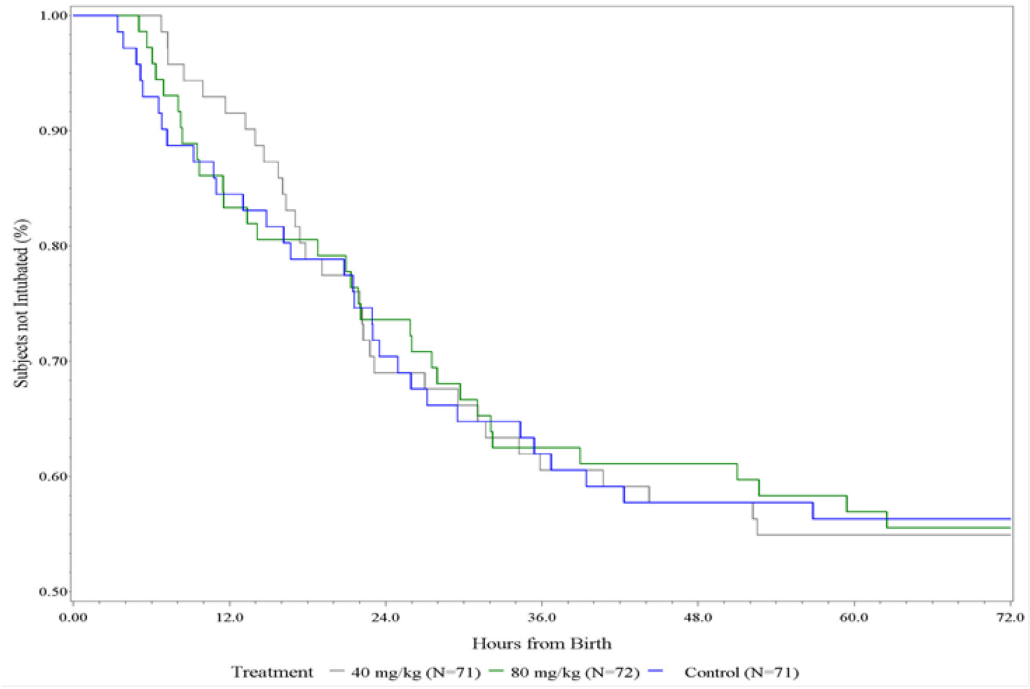
In Study 03-CL-1202, the incidence and pattern of AEs was similar in subjects who experienced treatment interruptions vs. those in whom treatment interruptions did not occur. All subjects with treatment interruptions continued to receive nCPAP at the level set by the subject's clinician: no unexpected losses or increases in nCPAP level were reported.

Efficacy

The overall results from the mITT did not show a difference in the primary outcome of CPAP failure requiring intubation. All 3 groups (40 mg TPL/kg, 80 mg TPL/kg, and nCPAP alone) had a CPAP failure rate of 44%, possibly due to treatment interruptions.

As was seen with the other studies, intubations in the active groups occurred late than in the nCPAP only group (Figure 2-4). The difference does not persist, however, and by 18 hours all three treatments had a similar number of intubations.

Figure 2-4. Time to Intubation from Randomization in Study 03-CL-1202 Modified Intent-to-Treat Population



Data source: Study 03-CL-1202, Summary Figure 1.1.1.

Unanticipated treatment interruptions occurred more frequently in Study 03-CL-1202 than in other studies, thus complicating the overall assessment of efficacy in this trial. Because most treatment interruptions were related to the clogging of a filter in the path of the liquid reconstituted lucinactant, they tended to occur later in the course of treatment. Thus, interruptions were more likely to occur in the 80 mg TPL/kg group (which required a single 50-min administration) than in the 40 mg TPL/kg group (which required a single 25-min administration). Because nCPAP Only control subjects did not receive study drug, they could not experience treatment interruptions. Other than being randomized to the 80 mg TPL/kg dose group, no other identifiable patient-related factor was associated with the occurrence of treatment interruptions.

A review of efficacy data where subjects with treatment interruptions removed demonstrated some evidence of efficacy. In this population of mITT without treatment interruptions, the overall rates of nCPAP failure were 44%, 32%, and 44% for 40 mg TPL/kg, 80 mg TPL/kg, and nCPAP Only, respectively; a relative reduction of 27% between 80 mg TPL/kg and nCPAP Only. Efficacy findings suggest that lucinactant for inhalation in conjunction with nCPAP may be beneficial when

administered as intended; however, these findings will need to be confirmed in further clinical studies.

BPD

For Studies 03-CL-1401 and 03-CL-1202 combined, AEROSURF decreased BPD incidence with statistically significant post-hoc p-values for Study 03-CL-1401 and for all subjects combined (Table 2-1).

Table 2-1. Incidence of BPD at All Doses

	26-28 Weeks PMA		28-32 Weeks PMA		All Subjects	
Definition	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.

In addition, BPD severity was assessed at doses ≥ 75 mg TPL/kg for infants in Studies 03-CL-1401 and 03-CL-1202. As with overall incidence, AEROSURF decreased BPD severity (Table 2-2).

Table 2-2. Severity of BPD at Doses ≥ 75 mg TPL/kg

Definition		AEROSURF (≥ 75 mg/kg) (N=88)	Control (N=95)	*p*-value
O_2 at 36 Weeks	Incidence	7 (8%)	16 (17%)	0.07
NIH definition	Mild	3 (3%)	4 (4%)	0.12
	Moderate	3 (3%)	4 (4%)	
	Severe	1 (1%)	8 (8%)	

† Chi-square test; *p-value ≤ 0.05.

These results demonstrate that AEROSURF may reduce the incidence and severity of BPD, while avoiding endotracheal intubation and potentially reducing the need for MV and supplemental oxygen (28).

Summary

The results from Studies 03-CL-1201, 03-CL-1401, and 03-CL-1202 demonstrate that delivery of reconstituted lucinactant as an aerosol using the ADS is feasible and that lucinactant for inhalation appears to be generally well-tolerated in neonates in this gestational age range with RDS, with no safety concerns yet identified. Assessment of clinical efficacy showed some preliminary evidence of effect but was complicated by the occurrence of unanticipated treatment interruptions which may have obscured a potential efficacy signal. Additional clinical studies are warranted.

3 STUDY DESIGN AND RATIONALE

3.1 Study Design

This study is a multinational, multicenter, double-blind (masked), parallel group, randomized, controlled study to investigate the safety and efficacy of lucinactant for inhalation (in conjunction with nCPAP) compared to nCPAP alone. The study design will include 2 parallel treatment groups (160 mg TPL/kg lucinactant for inhalation and nCPAP only) in preterm neonates 26 to 32 completed weeks PMA with RDS who are within the first 6 hours after birth, who had successful implementation of non-invasive mode of oxygen support (such as BiPAP or oxyhood) within 30 minutes of birth, and who are candidates for SRT (study nCPAP is strongly recommended as the initial mode of support). There will be 2 phases in the study: a primary phase through 36 weeks PMA and a longer-term follow-up phase through 12 months corrected age. Data will be analyzed and reported at the completion of each study phase.

Before study enrollment, legally authorized representatives will provide a signed informed consent form (ICF) for each potential subject. Qualification for study enrollment will be established after informed consent has been provided and after confirmation that the subject has met all of the inclusion criteria and none of the exclusion criteria. The clinical criteria for enrollment may be met prior to informed consent being obtained; however, no study-specific procedures that are not part of the usual standard care of the subject at the institution may be performed until the informed consent has been provided by a legally authorized representative of the subject.

Inclusion criteria to be met within the first 6 hours after birth include respiratory insufficiency with a requirement for nCPAP of 5 to 7 cmH_2O and an $FiO_2 \geq 0.25$ to ≤ 0.35 to maintain oxygen saturation as measured by pulse oximetry (SpO_2) of 90% to 95% for at least 15 minutes. As soon as study qualification has been confirmed and the informed consent is signed, subjects will be immediately randomized (in a 1:1 ratio) to 1 of the 2 treatment groups (active or control). Subjects will be enrolled by strata: 26 to 28 completed weeks PMA and 29 to 32 completed weeks PMA. Based upon the sizes of the patient populations and the prevalence of RDS in these populations, it is expected that approximately 10-15% of subjects will be 26 to 28 completed weeks PMA; however, stratification is being used to ensure balance of randomization at study sites and to ensure balance within each stratum.

In order to ensure correct functioning of the ADS and to reinforce study treatment procedures, the first 2 subjects at each site will be dosed open-label on active study treatment (160 mg TPL/kg

lucinactant for inhalation followed by 80 mg TPL/kg repeat treatments). All procedures for treatments and repeat treatments will be followed as are done for all other subjects.

Study therapy (lucinactant for inhalation or sham/control) must be initiated as soon as possible after randomization. Subjects for both active and sham treatments will be connected to the same setup (using the study nCPAP and study airway connector; see Section 8.7.3). Following completion of the setup, subjects will need to stabilize for at least 15 minutes. The start time for active treatment is the time at which the subject is connected to the ADS. The sham treatment will simulate a connection to the ADS. Thus, the start time for sham treatment (treatment initiation) is the time at which this simulated connection occurs; the stop time will be 110 minutes later (to account for an approximate 10 minutes to switch the syringe and cartridge in the active treatment group).

Subjects may be eligible to receive up to 3 repeat study treatments (active or sham) to which they are assigned; however, the dose of the active treatment will be 80 mg TPL/kg. Repeat treatments will be given as soon as 20 minutes from completion of the previous treatment up to 36 hours after randomization if subject meets repeat treatment criteria, unless it is unsafe to do so in the judgment of the PI, as described in Section 6.6. Subjects randomized to the control group will be continued on nCPAP alone but will receive repeated sham treatment to maintain study masking. Details on the ADS is outlined in Section 6.1.

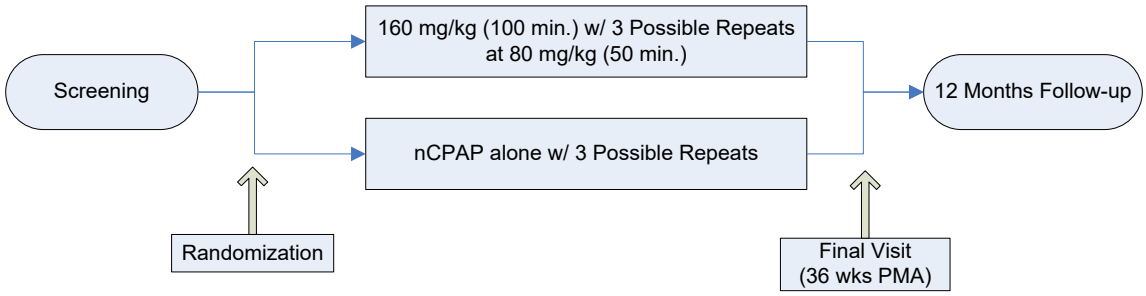
Treatment assignments, outside the first 2 open-label subjects who will receive active study treatment, will be masked from the PI; clinical and study staff (eg, site coordinator, bedside nurse), as applicable; sponsor, as applicable; and subject's parents/legal guardians. All enrolled subjects will receive study treatment in a NICU, a specialized care center staffed by neonatologists, nurses, and respiratory therapists who are experienced in the delivery of emergent care to the preterm neonatal population. Neonates in the NICU are continuously monitored using advanced and sophisticated monitoring equipment, and there is ready and immediate access to equipment, medications, and skilled personnel that may be needed to address emergent developments. Interventions such as endotracheal intubation, MV, and traditional surfactant administration will be readily available to all study subjects if clinically indicated in accordance with the high-level standard-of-care customary in the NICU.

Neonates will be followed for the primary phase efficacy and safety evaluations through 36 weeks PMA, hospital discharge, hospital transfer, or death (whichever occurs first). For the longer-term follow-up phase, neonates will be evaluated by phone at 6-months corrected age and at a visit at

12-months corrected age, at which time a physical examination will be performed, including an abbreviated neurologic assessment. (See also Section 8.)

A schematic diagram of the study design is displayed in Figure 3-1.

Figure 3-1. Schematic of Study Design for 03-CL-1702



3.2 Dose and Device Description and Rationale

In this study, approximately 65 subjects will be randomized to active treatment and will receive aerosolized lucinactant through the ADS in conjunction with nCPAP. Approximately 65 subjects will be randomized to the control group and will receive nCPAP alone with "sham" study drug treatment.

3.2.1 General Description and Rationale for the ADS

A full description of the ADS is given in Section 6.1. Briefly, reconstituted lyophilized lucinactant is pumped at high pressure and temperature through a capillary, which aerosolizes the lucinactant. The aerosolized lucinactant is propelled by gas flow and carried via an aerosol delivery tube where it joins the subject's nCPAP system, allowing administration of aerosolized surfactant while maintaining respiratory support with nCPAP. The current version of the ADS represents a "commercially equivalent" device and is an update from the prototype device used in all prior lucinactant for inhalation studies.

Unlike prior attempts to aerosolize surfactants with conventional nebulizers, the ADS may aerosolize lucinactant in sufficient quantities to affect a therapeutic response sufficient to avoid endotracheal intubation. A device that permits effective surfactant aerosolization to neonates while receiving nCPAP support for the treatment of RDS may improve the success of nCPAP therapy and better avoid the potential deleterious effects of endotracheal intubation and mechanical ventilation.

3.2.2 Rationale for Study Control

Preterm neonates who are treated for RDS initially with non-invasive ventilation (including nCPAP) are the appropriate controls for this study, since the addition of aerosolized surfactant would be the only difference in treatment in the active groups compared to the controls. Current guidelines call for the use of non-invasive ventilation such as nCPAP as an initial modality for the treatment of RDS in preterm newborns, with the goal of avoiding endotracheal intubation (3,4,5,6,11).

Initial treatment with brief intubation, surfactant delivery and extubation (the "INSURE" technique) or other forms of "minimally" invasive intratracheal (eg, the "LISA" or "MIST" techniques) or supraglottic (eg, via laryngeal mask airway) surfactant instillation represent potential alternative therapeutic strategies for SRT in RDS which would not demonstrate the effectiveness of aerosolized lucinactant in an isolated fashion, and thus would not be appropriate controls.

Each of the 4 components of lucinactant (see Section 6.2.1) plays a role in its biological activity. Aerosolized vehicles (eg, sterile water or saline) may have an adverse effect on pulmonary function. Thus, no inert placebo exists. Therefore, "sham" treatment, in which the ADS is brought to the subject's bedside but not used to deliver study drug, is the optimal control.

All study treatments (whether active or control) are given only if subjects are stable enough that they do not require intubation. Such subjects would typically be maintained on standard nCPAP or other forms of non-invasive ventilation. Since control/sham treatment is equivalent to standard care, it is ethical to administer for initial or repeat treatments.

3.2.3 Dosage Rationale

3.2.3.1 General Considerations in Dosage Selection

Lucinactant, administered as an intratracheal liquid bolus at a dose of 175 mg TPL/kg (5.8 mL/kg of a 30 mg TPL/mL suspension) has been demonstrated to be safe and effective in the prevention of RDS in preterm neonates at high risk for RDS and has been approved by the FDA (trade name SURFAXIN®, NDA 021746). However, SURFAXIN is not currently marketed based solely on business considerations (not as the result of any safety, efficacy, or quality concerns). However, the precise quantity of surfactant replacement required by any given neonate cannot be measured or known. The amount of surfactant needed by a neonate increases with alveolar surface area, which increases with weight and gestational age. The amount of endogenous surfactant available

to a neonate depends critically on gestational age and lung maturation, but also on a number of other immeasurable factors including lung inflammation and prenatal steroids. Although neonates born at a lower gestational age are likely to be more surfactant deficient compared with neonates born at higher gestational ages, dosing algorithms based on gestational age or birth weight would be inadequate to estimate the dose of exogenous surfactant that should be administered to adequately replete surfactant and thereby treat RDS.

Neonates at high risk for RDS are presumed to be substantially or wholly surfactant deficient; these neonates require immediate endotracheal intubation, SRT and MV. In contrast, the population of preterm neonates who can be sustained by nCPAP, rather than endotracheal intubation and MV, likely represent a broad spectrum of varying degrees of surfactant deficiency who may not require the full intratracheal dose of SRT. Study KL4-CPAP-01 (27) (Section 2.3.1) suggested an appropriate dosage of aerosolized lucinactant (using the Aeroneb® Pro Nebulizer System) for premature neonates with RDS supported with nCPAP could be in the range of 75 mg TPL/kg, substantially lower than the intratracheal bolus lucinactant dosage of 175 mg TPL/kg.

Inhalational delivery of drugs is extremely inefficient compared to most other modes of delivery. When delivered traditionally as an intratracheal bolus of liquid, it is highly likely that most, if not all, of the instilled surfactant will ultimately arrive at its site of action in the alveoli since surfactants tend to spread along surfaces. Studies in neonatal piglets have demonstrated that aerosolized surfactant is deposited in the lung much less efficiently than an equivalent intratracheal bolus (29) but with similar physiologic effects (30).

Delivery of an aerosol to the alveoli will vary depending on the characteristics of the device (eg, condensation within tubing or impaction within the device), the aerosol itself (eg, particle size and rate of administration), and the breathing characteristics of the individual neonate (eg, inspiratory and expiratory patterns and ratios, frequency, tidal volume). To reach the alveoli and be deposited there, inhaled particles typically require a diameter ≤ 5 µm. Ideally, the rate of aerosol administration is kept constant and similar to the neonate's inspiratory flow rate to maximize the amount of aerosol that is inhaled. Typically, inspiratory and expiratory patterns in preterm neonates vary from breath to breath, although are less variable than in older infants and children. Minute ventilation is the amount of air exchanged (inhaled and exhaled) in one minute and is calculated as the product of breathing frequency and tidal volume. Minute ventilation generally tends to be less variable than the pattern of individual breaths. Since minute ventilation is related to body surface area, which is in turn dependent on body weight (29,30), it can be used to estimate the theoretical maximum inhalable dose of aerosolized surfactant normalized to body weight. The

actual inhaled dose is likely to be less than the theoretical maximum since some aerosolized surfactant will be expelled during exhalation or will deposit in the naso- and oropharynx where it may then be swallowed.

3.2.3.2 Calculation of the Theoretical Inhaled Dose

The theoretical inhaled dose is the amount of aerosolized lucinactant predicted to be inhaled by the subject. This inhaled dose is a function of the concentration of lucinactant in the aerosol, the amount of aerosol inhaled by the subject (estimated by the subject's minute ventilation, assuming that all gas inhaled by the subject contains the same concentration of aerosol), and the duration of exposure to the aerosol. Thus, the inhaled dose can be estimated using the following equation:

$$\text{Inhaled Dose} = C \times \left({}^{Vm}\!/_{kg} \right) \times T$$

Where: C = Concentration of lucinactant in aerosol (in mg TPL/L)
Vm/kg = Minute ventilation normalized to body weight (in L/min/kg)
T = Dose duration (in minutes)

The aerosolized lucinactant is carried to the patient interface by a gas (generally a mix of air and supplemental oxygen). The rate of flow of the carrier gas was chosen to be 3 L/min, which represents the typical peak inspiratory flow rate expected in the target population. The emitted dose rate of the ADS has been previously estimated as 12.6 mg TPL/min, within the device specification of 9.7 to 19.8 mg TPL/min (nominal 14.4 mg TPL/min). The concentration of aerosolized lucinactant in the carrier gas (C) is the emitted dose rate (12.6 mg TPL/min) divided by the carrier gas flow rate (3 L/min).

$$C = \frac{12.6 \text{ mg TPL/min}}{3 \text{ L/min}} = 4.2 \text{ mg TPL/L}$$

The emitted dose of lucinactant for inhalation is the amount of aerosolized lucinactant delivered to the subject at the output of the aerosol tube where it joins the patient nCPAP interface. For a specific treatment duration, the emitted dose is the emitted dose rate multiplied by the dose duration.

Minute ventilation (Vm) of preterm neonates can be estimated based on body weight, as shown in Table 3-1. When normalized to body weight, minute ventilation of the subjects expected to enroll in this study (750 to 2250 g) can be approximated as 0.4 L/min/kg.

Table 3-1. Estimated Minute Ventilation of Preterm Neonates, by Weight

	Bide et al. (29)		Bhutani et al. (30)	
	Vm		Vm (50th percentile)	
Weight (g)	(L/min/kg)[1]	(L/min)	(L/min/kg)	(L/min)
750	0.527	0.3954	0.4	0.3000
1000	0.499	0.4990	0.4	0.4000
1250	0.478	0.5977	0.4	0.5000
1500	0.462	0.6927	0.4	0.6000
1750	0.448	0.7847	0.4	0.7000
2000	0.437	0.8742	0.4	0.8000
2250	0.427	0.9616	0.4	0.9000
2500	0.419	1.0472	0.3	0.7500
2750	0.411	1.1312	0.3	0.8250

[1] Calculated

Currently, the maximum run time for a single syringe is 50 minutes. Thus, based on the dose equation above (C × Vm × T), this yields a theoretical inhaled dose of approximately 80 mg TPL/kg (4.2 mg TPL/L × 0.4 L/min/kg × 50 min.) for a 50-minute treatment with a single syringe.

3.2.3.3 Rationale for Dosages Used in the Current Study

The dosages used in Studies 03-CL-1201, 03-CL-1401 and 03-CL-1202 were 25, 40, 50, 75, 80, 100 and/or 150 mg TPL/kg. From a practical standpoint, however, dosages > 80 mg TPL/kg were cumbersome to administer, requiring the prototype ADS system to be temporarily shut down to change the syringe.

In the modified ADS, two dosages of 80 mg TPL/kg can be administered without shutting down the device or risking de-recruitment of the neonate's lung. Thus, Windtree decided to develop and evaluate an initial dosage of 160 mg TPL/kg, with repeat doses of 80 mg TPL/kg if higher dosages are needed.

3.2.3.4 Nonclinical Experience Supporting Dose Rationale

Study MB 04-12812.01 evaluated the toxic effects of orally administered lucinactant in adult rabbits. A total of 14 daily doses of 600 mg TPL/kg lucinactant (20 mL/kg) or 20 mL/kg Tris/NaCl buffer were administered orally by gavage in 2 equal volumes (10 mL/kg) at 2- or 4-hour intervals to adult rabbits (2 males and 2 females per treatment group). A total of 8400 mg TPL/kg of lucinactant was administered enterally. No evidence of any toxic effect was found in any animals in this study.

Two completed nonclinical animal toxicology studies in pre-weaned rabbits (Study N107662) and pre-weaned rats (Study N107663) evaluated the acute toxicity of inhaled lucinactant (aerosolized by CAG technology). Rabbits and rats were exposed to aerosol on 2 consecutive days by a nose-only inhalation exposure system. Aerosolized lucinactant low-, mid-, and high-dose groups were compared with air control and vehicle. Aerosolized lucinactant dose selections were based on the following; (1) potential human exposure (2) existing toxicity data (3) limitations imposed by the animal model (4) the exposure apparatus and its procedures, and (5) the stability of the experimental atmosphere. A total of 2716 mg TPL/kg of lucinactant aerosol was administered to rabbits over 2 days, and a total of 4252 mg TPL/kg of lucinactant aerosol was administered to rats over 2 days. A maximum feasible dose of aerosolized lucinactant was established based on these parameters and no observed adverse effect levels (NOAELs) were established to ensure adequate safety in preterm neonates.

These nonclinical studies (Studies MB 04-12812.01, N107662, N107663) provide a safety margin of > 10:1 (rats) or > 6:1 (rabbits) for the highest dose (400 mg TPL/kg) to be employed in the clinical program, whether delivered to the lungs or swallowed. It should be noted that the dosage of lucinactant (SURFAXIN) approved by FDA (NDA 021746) for intratracheal administration is 175 mg TPL/kg, with up to 3 repeat treatments (total dose of 700 mg TPL/kg) over 24-48 hours.

3.2.3.5 Clinical Experience Supporting Dose Rationale

Lucinactant for inhalation has been studied in 3 phase 2 trials: 03-CL-1201 (preterm neonates 29-34 weeks PMA), 03-CL-1401 (preterm neonates 26-28 weeks PMA), and 03-CL-1202 (preterm neonates 28-32 weeks PMA).

Outcomes with a dose of 80 mg TPL/kg can be estimated by pooling the results of dosages immediately below (75 mg TPL/kg) and above (100 mg TPL/kg) in Study 03-Cl-1201 (see Section 2.3.2 for full description of this study). AEs, SAEs and complications of prematurity occurred at rates in these two groups similar to the remainder of the active cohort and controls, suggesting 80 mg TPL/kg would be well-tolerated. Dosages of 75 and 100 mg TPL/kg reduced nCPAP failure: of the 15 subjects treated with these dosages, 4 (27%) had nCPAP failure within 72 hours of life vs 53% of pooled controls (Figure 3-2). Further, dosages of 75 and 100 mg TPL/kg appeared to delay nCPAP failure as well, since none of the active subjects had nCPAP failure within 6 hours of dosing vs 18% of pooled controls (Figure 3-2, Figure 3-3). The reduction in nCPAP failure rate at 72 hours was seen both in subjects with lower (29-31 weeks PMA) and higher (32-34 weeks PMA) gestational age (Figure 3-4). These results suggest 80 mg TPL/kg dosage is likely to be effective.

Figure 3-2: Cumulative Incidence of Intubation for any Reason in Study 03-CL-1201

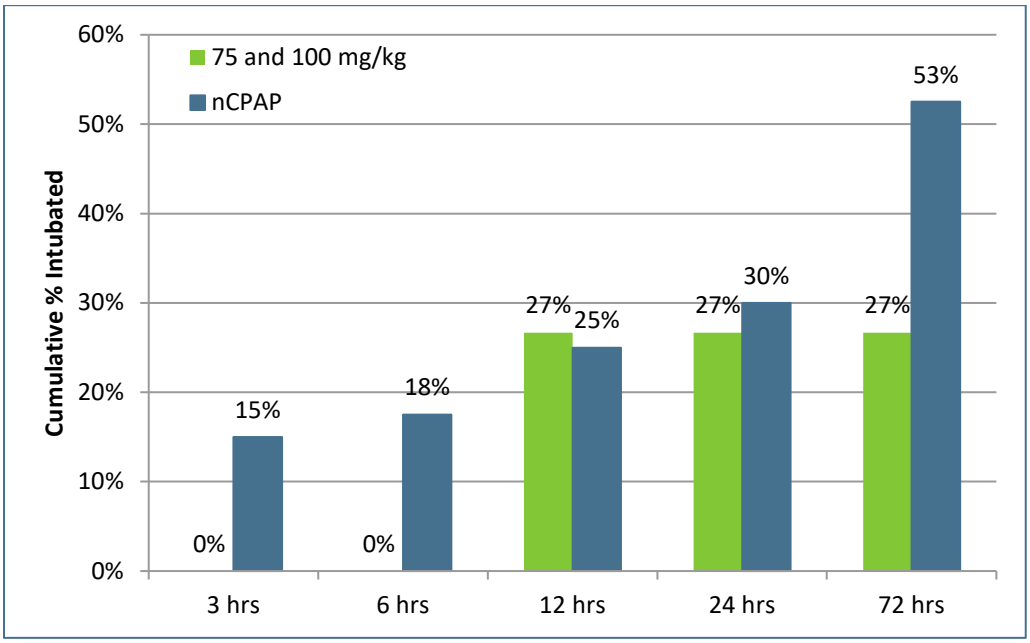


Figure 3-3: Kaplan-Meier Plot – Proportion of Subjects Not Intubated Study 03-CL-1201

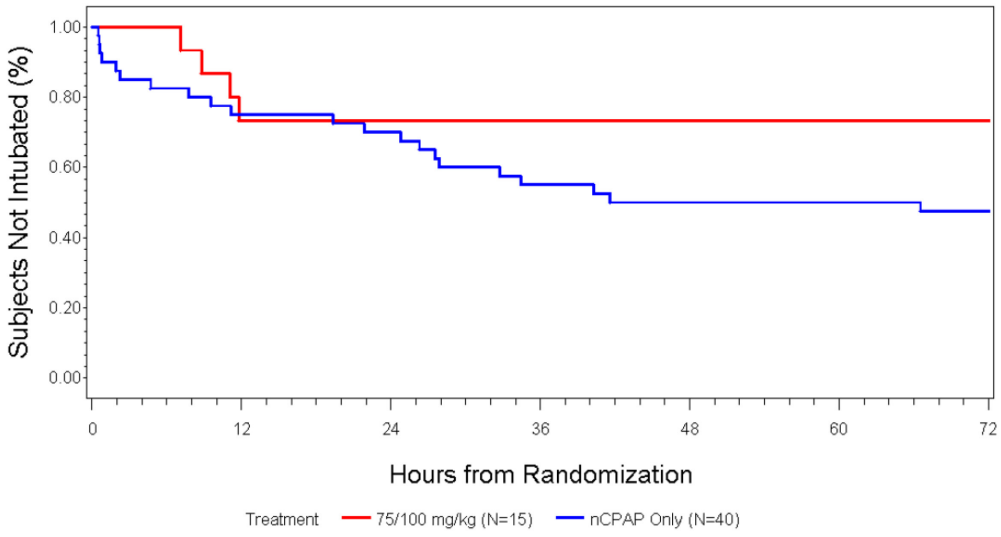
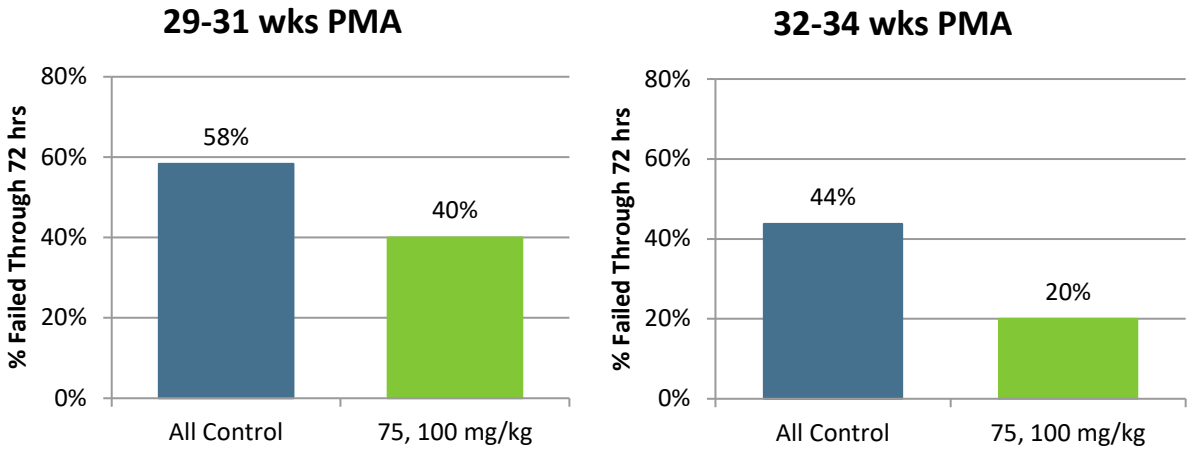
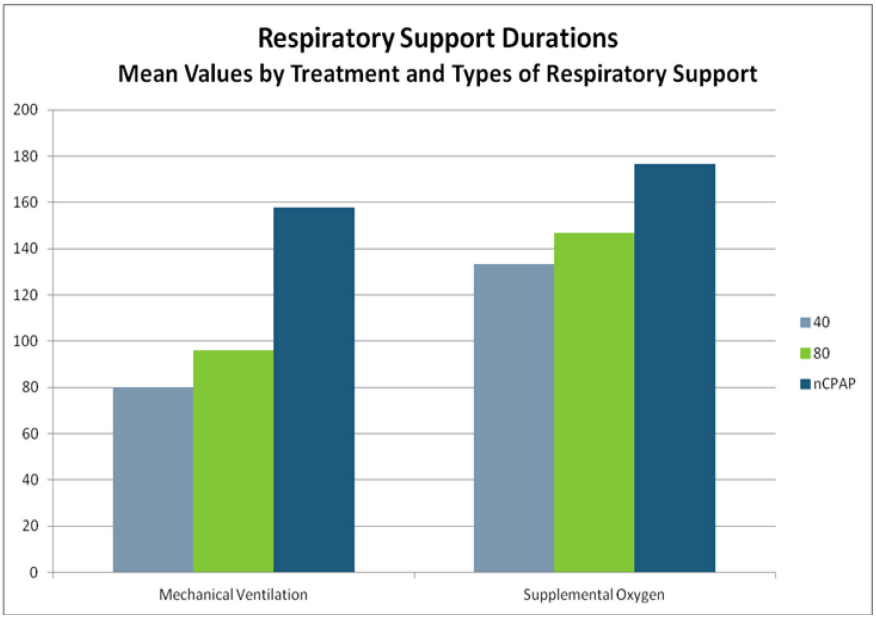


Figure 3-4: Incidence of Intubation for any Reason by Gestational Age Group Study 03-CL-1201



For Study 03-CL-1202, the overall results from the mITT did not show a difference in the primary outcome of CPAP failure requiring intubation. All 3 groups (40 mg TPL/kg, 80 mg TPL/kg, and nCPAP alone) had a CPAP failure rate of 44%. However, the results may show a clinically meaningful benefit of lucinactant for inhalation in subjects who ultimately failed nCPAP and required subsequent intubation for SRT treatment and MV. When these subjects were evaluated for the amount of respiratory support they required (time on MV and time on supplemental oxygen) the patients treated with lucinactant for inhalation required a numerically shorter duration of support (Figure 3-5).

Figure 3-5. Respiratory Support (hours) in Subjects Who Failed nCPAP Study 03-CL-1202

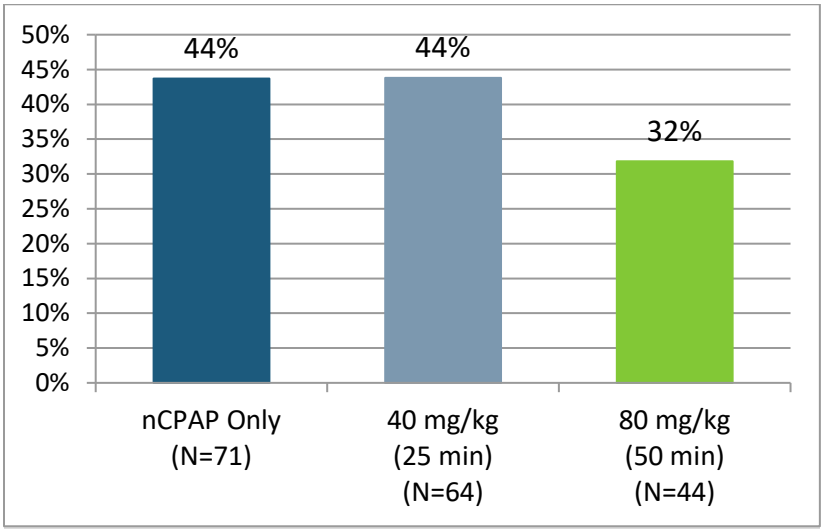


Unanticipated treatment interruptions occurred more frequently in Study 03-CL-1202 than in other studies, thus complicating the overall assessment of efficacy in this trial. Because most treatment interruptions were related to the clogging of a filter in the path of the liquid reconstituted lucinactant, they tended to occur later in the course of treatment. Thus, it is not surprising that interruptions were more likely to occur in the 80 mg TPL/kg group (which required a single 50-min administration) than in the 40 mg TPL/kg group (which required a single 25-min administration). Because nCPAP Only control subjects did not receive study drug, they could not experience treatment interruptions. Other than being randomized to the 80 mg TPL/kg dose group, no other identifiable patient-related factor was associated with the occurrence of treatment interruptions.

In order to examine the effects of treatment when successfully delivered, the results for Study 03-CL-1202 were examined for subjects without treatment interruptions. Considering only subjects who had no treatment interruptions or received adequate dosing, nCPAP failure occurred in 32% in the 80 mg TPL/kg group compared to 44% in both the 40 mg TPL/kg and nCPAP Only groups (Figure 3-6). This represents a 12% absolute and a 27% relative reduction in nCPAP failure in the 80 mg TPL/kg group. Thus, the results of this trial show a similar pattern of reduction in nCPAP

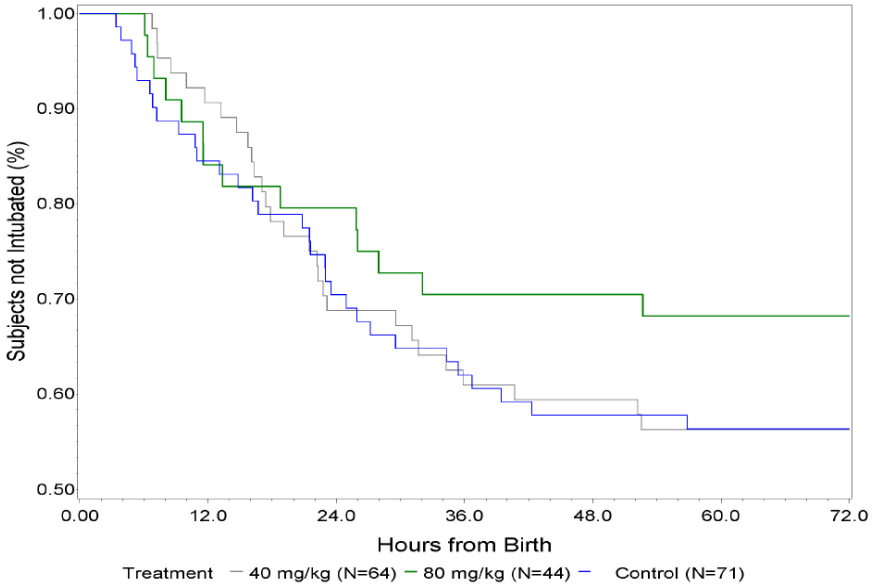
failure to that seen in 03-CL-1201 in a similar gestational age range population. Less impact on nCPAP failure was seen in the 40 mg TPL/kg dose, consistent with Studies 03-CL-1201 and 03-CL-1401 which established an apparent efficacy threshold of at least 45 mg TPL/kg.

Figure 3-6. Incidence of nCPAP Failure in Subjects without Treatment Interruptions in Study 03-CL-1202 (mITT)



Interestingly, in all 3 Phase 2 studies (blinded and unblinded), intubation occurred later in subjects in both active groups compared to control. This initial early effect dissipated in the 40 mg/kg group (Figure 3-7) and is suggestive that lucinactant for inhalation has an initial physiological impact but had inadequate dosing during this time period to prevent progression of RDS.

Figure 3-7. nCPAP Failure over Time in Study 03-CL-1202 (mITT without Treatment Interruptions)



Subjects in this study may receive up to 3 repeat treatments, meaning that the subjects could receive a total of 400 mg TPL/kg over approximately 36 hours. Repeated treatments of intratracheal surfactant are often necessary and beneficial in neonates with RDS (1). In study 03-CL-1201 (Section 2.3.2.1), 3 subjects received repeated treatments: 1 subject in the 100 mg TPL/kg group (total dose of 200 mg TPL/kg) and 2 in the 150 mg TPL/kg group (total dose of 300 mg TPL/kg). No AEs or ADEs related to study treatment occurred with repeat dosing in these subjects. For comparison, the dosage of lucinactant (SURFAXIN) approved by FDA for intratracheal administration is 175 mg TPL/kg, with up to 3 repeat treatments (total dose of 700 mg TPL/kg) over 24-48 hours. In addition, neonates with meconium aspiration syndrome have received doses of SURFAXIN 120 mg TPL/kg (31) by whole lung lavage, and adults with acute respiratory distress syndrome have received doses up to 8.55 g (114 mg TPL/kg) by bronchoscopic segmental lung lavage (32).

3.2.4 Risk and Benefit of Study Interventions

Risks and benefits of this study must be considered within the context of treating RDS in preterm infants, which carries substantial risk of morbidity and mortality. These infants often require intratracheal SRT as well as MV to survive; however, both MV and endotracheal intubation are

themselves associated with morbidity and mortality in this fragile population. Various types of non-invasive ventilation, including nCPAP, have been used to avoid endotracheal intubation and MV. However, nCPAP will be unsuccessful in about one third to one half of neonates with RDS, who will then require invasive MV and endotracheal intubation to receive SRT. Survivors are at risk of complications of prematurity including BPD, retinopathy of prematurity (ROP), IVH and NEC.

Lucinactant for inhalation is a drug-device combination product, with separate risks and benefits associated with the device and the drug. The ADS operating principle is based on the principles of a heated nebulizer, which has been well characterized. The ADS risk evaluation and resulting mitigation strategies were conducted against and met ISO 14971 requirements.

3.2.4.1 Risk and Benefit of Control Treatment

As described in Section 6.4.2, control treatment involves continuing subjects on nCPAP while the ADS is delivered to the bedside (in a blinded fashion) but is not used ("sham" treatment). Thus, control/sham treatment is identical to standard therapy with nCPAP. As described in Section 3.2.2, control/sham treatment in subjects who do not require endotracheal intubation is ethical.

Known risks of standard nCPAP include nasal irritation/breakdown of the skin around the nose, apnea, oxygen desaturation, and air leak (eg, pneumothorax). Air leak with nCPAP has been reported in 3 to 47% of preterm neonates and may be somewhat more common in neonates with greater gestational age (Section 2.1.1). The risk of requiring endotracheal intubation and SRT has been reported as 33-67% (Section 2.1.1). Risks of nCPAP in the prior clinical study using the ADS (Study 03-Cl-1201, Section 2.3.2) were consistent with those reported in the literature.

Standard nCPAP and, therefore, control treatment, has the benefit of providing respiratory support without the potential complications of invasive MV. The important outcome of survival without BPD is equal to or more frequent with nCPAP compared to with traditional treatment with endotracheal intubation and SRT (Section 2.1.1).

3.2.4.2 Risks of Active Treatment and the AEROSURF Delivery System

Since the ADS delivers lucinactant for inhalation via conventional nCPAP, active treatment would include the same risks and benefits of respiratory support with standard nCPAP therapy described above in Section 3.2.4.1. Active treatment would carry the additional risks and benefits of aerosolized SRT with lucinactant for inhalation.

Known risks of standard nCPAP include nasal irritation/breakdown of the skin around the nose, apnea, oxygen desaturation, and air leak (eg, pneumothorax). Air leak with nCPAP has been reported in 3 to 47% of preterm neonates and may be somewhat more common in neonates with greater gestational age. The risk of requiring endotracheal intubation and SRT has been reported as 33-67%. Risks of nCPAP in the prior clinical study using the ADS (Study 03-Cl-1201) were consistent with those reported in the literature.

Lucinactant for inhalation is the reconstituted form of a lyophilized liquid surfactant (SURFAXIN); therefore, the known class risks of SRT with liquid surfactant via the intratracheal route may be applicable. These risks are described in the Investigator's Brochure and the SURFAXIN Package Insert, and include acute changes in lung compliance, bradycardia, oxygen desaturation, and airway obstruction. Rates of these adverse reactions and complications of prematurity were similar with SURFAXIN as with comparator surfactants. Pulmonary hemorrhage has been reported with intratracheal SRT, including with SURFAXIN.

In a prior clinical study using aerosolized lucinactant for inhalation via the ADS (Study 03-Cl-1201, Section 2.3.2), the incidence of AEs was similar in subjects receiving active treatment compared to controls and were as expected for this population of premature neonates. The 3 most common AEs were neonatal jaundice, constipation and neonatal apnea, and the 3 most common peri-dosing events were transient desaturation in 5 (13%) subjects, nasal irritation in 2 (5%) subjects, and vomiting in 2 (5%) subjects. Obstruction of the nares or upper airway by condensed aerosol is a theoretical risk but was not observed in Study 03-CL-1201. To mitigate the risk of airway obstruction, all subjects were continuously attended by a qualified clinician during dosing and are continuously monitored for SpO_2 and transcutaneous PCO_2. Although the drug product is heated during aerosolization, it cools to 23-38° C during delivery and the ADS will shut down if aerosol temperature is > 38° C; thermal injury to neonates was not observed in Study 03-CL-1201. The volume of aerosolized fluid administered to neonates could, in theory, affect fluid and electrolyte balance; however, no such problems were observed in Study 03-CL-1201 and electrolytes will be assessed in the present study.

Risk of air leak was 23% in active treatment subjects vs 18% (23% based on independent radiologist review) among controls. Experience with repeated dosing is limited to 3 subjects in Study 03-CL-1201; although each received dosages higher than planned for the present study, incidence of AEs in these 3 subjects was similar to that in the remainder of the cohort.

Automatic shutdown of the ADS was uncommon in study 03-CL-1201 (10% of subjects) and mostly (3/4 shutdowns) occurred at the highest dosage; only 1 shutdown occurred at a dosage (75

mg TPL/kg) similar to that proposed in the present study. All shutdowns resulted from error codes, and none resulted in any AE being reported. All subjects maintained nCPAP and inspiratory flow during active treatment, demonstrating the important safeguard that nCPAP is maintained even if the ADS fails. One ADE of nasal inflammation occurred; no other device-related performance issues resulted in any harm to subjects. A complete qualitative risk assessment has been completed to identify and mitigate potential safety risks associated with use of the ADS.

In a phase 2b study using lucinactant for inhalation (Study 03-CL-1202), most subjects (94% and 93% for the active and control groups, respectively) experienced at least one AE. The most common TEAEs were jaundice (16 [44%] subjects), anaemia neonatal (5 [14%] subjects), and apnoea neonatal (5 [14%] subjects). No other TEAE was experienced by at least 5 subjects. A total of 30 active subjects reported 43 SAEs, and a total of 20 control subjects reported 30 SAEs. A total of 22 subjects reported 29 ADEs; no ADEs were considered serious or were unexpected. Two subjects in the nCPAP Only group died during the study, along with 1 subject in the 80 mg/kg group and no subjects in the 40 mg/kg group.

As would be expected, active subjects experienced more peri-dosing events than controls; there was no clear relationship between dosage and incidence of peri-dosing events among the active subjects.

Overall, the number of subjects with air leaks is lower than in prior clinical trials; air leak incidence was lower in the 80 mg/kg group than in the 40 mg/kg group (Table 3-2).

Table 3-2. Number (%) of Subjects with Air Leaks in Study 03-CL-1202

	40 mg/kg (N=70)	80 mg/kg (N=72)	nCPAP Only (N=71)
Number of subjects with an air leak	7 (10%)	6 (8%)	10 (14%)
Type of air leak	7 (10%)	6 (8%)	10 (14%)
Pneumothorax	7 (10%)	6 (8%)	9 (13%)
PIE	1 (1%)	0 (0%)	3 (4%)
Pneumomediastinum	1 (1%)	0 (0%)	1 (1%)

Data source: Study 03-CL-1202 Summary Table 6.2

There are no clinically important differences between subjects who received the active treatment compared to results for subjects who received control for complications of prematurity.

3.2.4.3 Benefits of Treatment with the AEROSURF Delivery System

Treatment with the ADS combines the potential benefits of treatment with aerosolized SRT with the known benefits of treatment with nCPAP. Traditional intratracheal SRT reduces mortality and morbidity in in preterm neonates with RDS. Aerosolized SRT has the potential to address RDS and these other complications of prematurity in a similar fashion. Standard nCPAP has the benefit of providing respiratory support without the potential complications of invasive MV. The important outcome of survival without BPD is equal to or more frequent with nCPAP compared with traditional treatment with endotracheal intubation and SRT.

3.2.4.4 Alternatives to Study Treatment

Alternative approaches to treating neonates with (or at risk for) RDS, as described in Sections 2.1 and 3.2.2, include attempting to support the neonate solely with a form of NIV (including nCPAP) and without SRT; supporting the neonate with NIV and reserving intratracheal SRT (using various techniques) only for those who require intubation; and the traditional approach of supporting the neonate with invasive MV and intratracheal SRT. As described in Section 3.2.4.1 above, the former 2 approaches are nearly identical to control treatment in the present study. Each of these approaches is supported by international guidelines (3,4,5,6,11), and no strategy has yet been demonstrated as being superior in neonates who do not require immediate intubation.

Antenatally, mothers of premature infants are often given systemic corticosteroids to accelerate the fetus' lung development, which reduces but does not eliminate the risk of RDS.

3.2.4.5 Summary of Risk-Benefit Assessment

In summary, the potential benefit of aerosolized reconstituted lucinactant delivered via the ADS is greater than the potential risk, especially when that risk is considered in the context of the risks of standard care of the premature newborn, including those of nCPAP. Further clinical study of this therapy in premature infants is therefore justified.

3.3 Study Duration

It is expected that recruitment will occur over a period of approximately 8 to 9 months. It is estimated that the last subject enrolled will complete 36 weeks PMA approximately 10 months from the time of the first subject enrolled.

Any adverse findings by the Data Monitoring Committee (DMC) may result in an extension of the study duration, early study closure, or early withdrawal of study subjects (Section 7).

3.3.1 Duration of Subject Study Participation

The total duration of study participation for each subject in the primary phase of the study will be from enrollment (≤ 6 hours from birth) to 36 weeks PMA (or 28 days of life, whichever occurs last). Each subject will participate in a follow-up phase through 12 months corrected age (12 months after the subject's anticipated full-term due date [40 weeks PMA]). Subjects who complete all assessments and procedures up to and including the Final Visit (to occur at 36 weeks PMA, hospital discharge, or hospital transfer, whichever occurs first) will be considered study completers. Details regarding subjects who withdraw from the study before completion are provided in Section 10.

Study participation will consist of the following study phases and periods (assessments, procedures, and visits occurring in each of these phases can be found in Section 1.2):

Primary Phase:

- Screening Period: To occur in a timely manner to allow for study randomization ≤ 6 hours from birth.
  - Study consent must be completed before any study-specific screening procedures that would not otherwise be performed in accordance with standard of care and local institutional practices.
- Primary Period: Time of start of initial treatment (T_0 on study) to 72 hours of life.
- Extended Period: > 72 hours of life to Study Day 7.
- Final Period: Study Day 8 to Final Visit at 36 weeks PMA (± 2 days), death, hospital discharge, or hospital transfer (whichever occurs first); however, subjects must remain in the study until 28 days of life (ie, 36 weeks PMA ± 2 days or 28 days of life, whichever occurs last).

Longer-Term Follow-Up Phase:

- Longer-Term Follow-Up Period: Evaluations occur at 6- and 12-months corrected age.

4 STUDY OBJECTIVES AND ENDPOINTS

This study is designed to investigate the safety and efficacy of lucinactant for inhalation in preterm neonates 26 to 32 completed weeks PMA. Efficacy and safety will be based on clinical evaluations (see Section 8). The endpoints specified are similar to those in Protocols 03-CL-1201, 03-CL-1401, and 03-CL-1202, to allow for potential comparison and pooling of results.

4.1 Objectives

To evaluate the safety and efficacy of lucinactant for inhalation delivered by the next generation ADS device in conjunction with nCPAP, in comparison to nCPAP alone, in preterm neonates with RDS, as assessed by the incidence of and time to respiratory failure due to RDS in the first 72 hours and through 28 days of life, oxygen saturation and use of supplemental oxygen, all-cause mortality through 28 days of life, the incidence of bronchopulmonary dysplasia (BPD) at 36 weeks PMA, and the duration of mechanical ventilation. In addition, this study will evaluate the device performance and the ability to administer up to 3 lucinactant for inhalation repeat treatments.

4.2 Estimand

The primary estimand for this study is the occurrence of intubation for the purpose of mechanical ventilation or surfactant administration in preterm neonates 28 to 32 weeks PMA in the modified intent-to-treat (mITT) population (all randomized subjects that received study medication). Intercurrent events include 1) treatment administration interruptions and 2) intubations for reasons other than MV or surfactant administration. Intercurrent events will evaluated using the treatment policy, hypothetical, and principal stratum strategies. Details on the implementation of the different strategies are provided in Section 13.

4.3 Efficacy Endpoints

4.3.1 Primary Endpoint

The primary endpoint for this study is the number of subjects with respiratory failure due to RDS or death within the first 28 days of life. Respiratory failure due to RDS is defined as intubation (including intratracheal catheter placement) for MV and/or surfactant administration.

Respiratory failure due to RDS or death will be categorized as follows:

- Early respiratory failure: Respiratory failure or death occurring ≤ 72 hours after birth
- Late respiratory failure: Respiratory failure or death occurring > 72 hours and ≤ 28 days after birth

Subjects meeting the criteria of respiratory failure due to RDS must continue to be followed for all safety evaluations as outlined in Section 1.2 until the time the subject completes the study or withdraws (Section 10.2).

4.3.2 Key Secondary Endpoints

The key secondary endpoints of this study include the evaluation of the following:

1. Respiratory failure through 72 hours and 28 days of life
2. Time to respiratory failure through 72 hours and 28 days of life
3. BPD and survival without BPD at 36 weeks PMA
4. Severity of BPD at 36 weeks PMA
5. Oxygen saturation and use of supplemental oxygen
6. All-cause mortality through 28 days of life and 36 weeks PMA

4.3.3 Other Secondary Endpoints

Other secondary endpoints of this study include the evaluation of the following:

1. Common complications of prematurity through 36 weeks PMA (IVH, periventricular leukomalacia [PVL], pulmonary hemorrhage, apnea, NEC, patent ductus arteriosus [PDA], acquired sepsis, ROP).
2. Duration of MV and oxygen requirement through 36 weeks PMA
3. Changes in FiO_2, PCO_2, and SpO_2 over the first 72 hours of life, and over the first 7 days of life for FiO_2
4. Number/duration of and reason for re-hospitalization and urgent care visits through 12 months corrected age.
5. Respiratory medications through 12 months corrected age.

4.4 Safety Endpoints

The following safety measures are to be documented in the electronic case report form (eCRF) in accordance with timings outlined in Section 1.2:

1. All-cause mortality through 28 days of life (date and time of death, if applicable)
2. AEs, including adverse device effects (ADEs) and AEs of special interest including AEs during the dosing period, complications related to placement of bi-nasal prongs, and air leak (Section 9). AEs that are ongoing at 36 weeks PMA will be followed for an additional 30 days
3. Concomitant medications (Section 8.6)
4. Use of respiratory support and supplemental O_2 (Section 8.7), including the following:
    a. Need for endotracheal intubation and MV
    b. Mode of respiratory support, including oxygen only (without positive pressure)
5. Physical examinations (Section 8.2)
6. Assessments of the following:
    a) Vital signs (Section 8.1.1)
    b) O_2 saturation, as determined by pulse oximetry (SpO_2) (Section 8.1.2)
    c) Chest radiography prior to intubation (Section 8.3)
7. Monitoring of PCO_2 and FiO_2 (Section 8.1.2)

5 STUDY POPULATION SELECTION

5.1 Study Population

This study population will be comprised of preterm neonates $26^{0/7}$ to $32^{6/7}$ completed weeks PMA who are receiving care in a NICU and are receiving nCPAP as the primary support modality for RDS. This study is anticipated to enroll approximately 130 preterm neonates (approximately 50% in each treatment group) who are candidates for SRT and nCPAP. Subjects will be enrolled by strata: subjects $26^{0/7}$ to $28^{6/7}$ completed weeks PMA and subjects $29^{0/7}$ to $32^{6/7}$ completed weeks PMA.

The study population will be randomized in a 1:1 ratio into 1 of 2 treatment groups (see Section 6.4).

5.2 Inclusion Criteria

Each subject must meet all of the following inclusion criteria to be enrolled in this study:

1. Signed ICF from legally authorized representative. Where allowed, it is recommended that consent is obtained antenatally.
2. Gestational age of $26^{0/7}$ to $32^{6/7}$ weeks PMA.
3. Successful implementation of non-invasive support or ventilation within 30 minutes of birth.
4. Spontaneous breathing.
5. Investigator determination of RDS. A chest x-ray should be obtained before treatment to confirm the diagnosis.
6. Within the first 6 hours after birth, requires an nCPAP of 5 to 7 cm H_2O that is clinically indicated for at least 15 minutes with an FiO_2 of ≥ 0.25 to ≤ 0.35 to maintain SpO_2 of 90% to 95%. Transient (< 5 minutes) FiO_2 excursions outside this range do not reset the time requirement.

5.3 Exclusion Criteria

Subjects meeting any of the following exclusion criteria may not be enrolled in this study:

1. A heart rate that cannot be stabilized above 100 bpm within 5 minutes of birth
2. Recurrent episodes of apnea requiring positive pressure ventilation (PPV) administered manually or mechanically through any patient interface
3. A 5-minute Apgar score < 5

4. Major congenital malformation(s) or craniofacial abnormalities that preclude the use of nCPAP, diagnosed antenatally or immediately after birth
5. Clinically significant diseases or conditions other than RDS which could potentially interfere with cardiopulmonary function (eg, congenital heart disease, hydrops fetalis or congenital infection)
6. A known or suspected chromosomal abnormality or syndrome
7. Premature rupture of membranes > 3 weeks
8. Hemodynamic instability requiring vasopressors or steroids for hemodynamic support and/or presumed clinical sepsis
9. A need for intubation and/or invasive MV at any time before enrollment into the study
10. The administration (or plan for administration) of any the following:
    a) Another investigational agent or investigational medical device
    b) Any other surfactant agent
    c) Systemic corticosteroids (other than antenatal steroids)
11. Presence of air leak (pneumothorax, pneumomediastinum, pneumopericardium, subcutaneous emphysema, or definite evidence of PIE) on the baseline chest radiograph, or diagnosed via ultrasound or illumination.

6 STUDY TREATMENT DOSING AND ADMINISTRATION

Preterm neonates who meet all inclusion criteria and no exclusion criteria will be considered to be potential subjects. As soon as study qualification has been confirmed and parental consent obtained, subjects will be randomized to 1 of 2 treatment groups. Time to treatment is potentially an important factor in the success of non-invasive delivery of surfactant. Because of this and other operational factors, antenatal consent should be obtained where permitted. Subjects for which parental consent has been obtained but are not randomized are considered screen failures.

All subjects will receive standard neonatal care in the NICU. Subjects randomized to the active group and the first 2 subjects at each site will receive reconstituted lucinactant delivered via the ADS in conjunction with nCPAP. Subjects randomized to the control group will receive nCPAP only. In order to maintain masking, control subjects will receive "sham" study drug treatment: the ADS will be brought to the bedside but will not be used and no active study drug will be administered. All subjects, including controls, may receive up to 3 repeat treatments if repeat treatment criteria are met. Subjects randomized to the active treatment group may be administered up to an additional 3 treatments of lucinactant for inhalation within 36 hours of randomization. Subjects randomized to control may receive up to an additional 3 sham treatments while receiving nCPAP within 36 hours of randomization.

To maintain masking, study treatment will occur behind a visual barrier. Each site will develop a site-specific blinding plan based upon general procedures provided by Windtree. All staff designated as "blinded" will not be allowed to observe preparation of study materials, setup of the device, or to observe the subject during study treatment through discontinuation and removal of equipment unless an emergent condition develops. The sponsor (as applicable) and the subject's legally authorized representative will also remain masked. (See also Section 6.6.) For the first 2 open-label active study treatments, blinding procedures should still be followed to ensure the feasibility of the site's blinding plan.

If at any point during the delivery of lucinactant for inhalation a potential safety risk to the subject is identified, aerosolization must be discontinued and local NICU procedures followed to ensure the safety of the subject. Any significant clinical findings or observations must be documented and communicated to Windtree at the earliest time point possible.

6.1 AEROSURF Delivery System

The ADS creates and delivers aerosolized reconstituted lucinactant via 4 durable modules (Figure 6-1): the touch screen interface (also called the operator interface module), the syringe pump

module, the aerosol delivery module, and the power module; and 3 disposable system elements (Figure 6-2): the cartridge, the aerosol tube set, and the syringe. The ADS is designed for bedside use and is mounted on a wheeled pole for easy transport.

Figure 6-1. The AEROSURF Delivery System – Durable

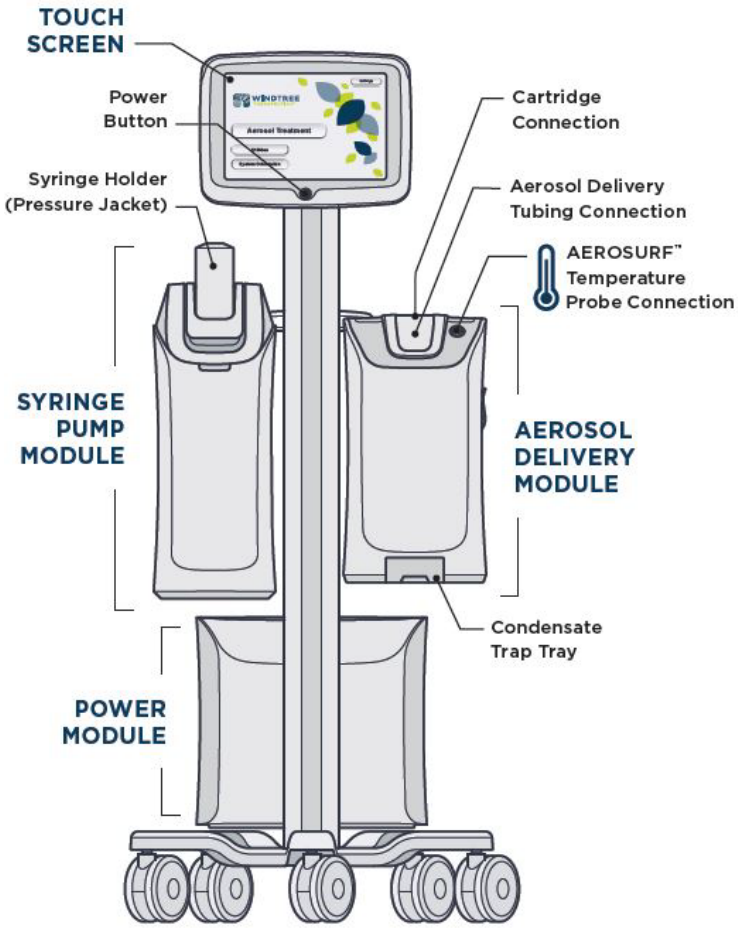
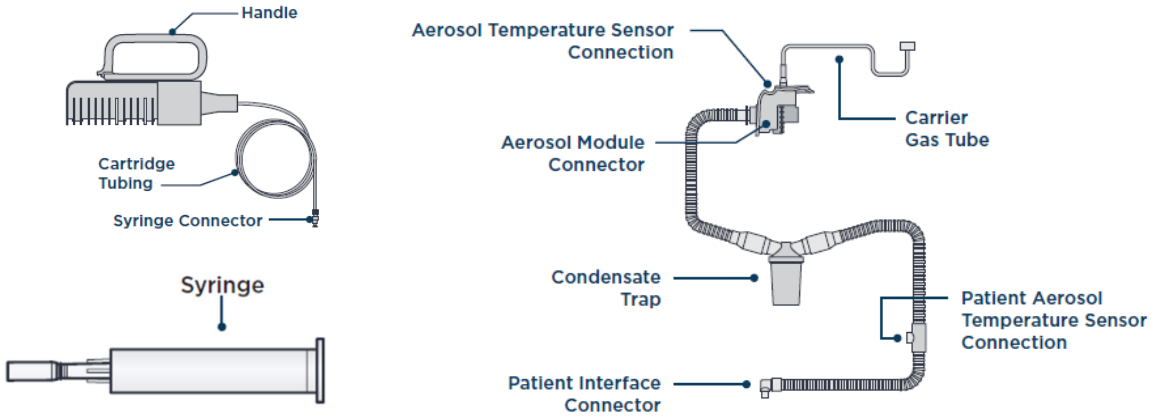


Figure 6-2. The AEROSURF Delivery System – Disposables



Details for study drug preparation and ADS operation are provided in the study manual and in the ADS Operator's Manual. Briefly, lyophilized drug is reconstituted immediately before use by adding 10 ml of sterile water for injection to each of 7 vials of lyophilized lucinactant, after which the vials are gently inverted to mix the suspension. The vials are drawn up into the provided syringe, which is then loaded into the syringe pump module. The ADS is brought to the subject's bedside and connected to the subject's nCPAP via the patient interface connector. Carrier gas flow through the ADS is started at 3 L/min while the nCPAP gas flow is reduced by 3 L/min, which allows nCPAP to be maintained during treatment.

The ADS aerosolizes reconstituted lucinactant through heat and pressure created within the cartridge. Together, the 4 modules, along with the disposable system elements, produce, control, and monitor the key elements necessary for the aerosolizing lucinactant.

A complete qualitative risk assessment has been completed to identify and mitigate potential safety risks associated with use of the ADS and is described in the Investigators' Brochure.

6.2 Identity of Investigational Drug Product

The complete list of ingredients for the drug product is shown in Table 6-1.

6.2.1 Formulation of Study Drug

The drug product (lyophilized lucinactant) is supplied as a sterile, white, liposomal powder consisting of a 21-amino acid hydrophobic synthetic peptide, (sinapultide, KL_4 peptide), the phospholipids dipalmitoyl-phosphatidylcholine (DPPC) and palmitoyloleoyl-

phosphatidylglycerol, sodium salt (POPG, Na), and the fatty acid palmitic acid (PA). Immediately before dosing, the lyophilized product is reconstituted with sterile water for injection to a concentration of 30 mg TPL/ml. Reconstituted product should be administered to a study subject (treatment initiated) within 5 hours of reconstitution (33).

Table 6-1. Drug Description

Ingredient	Amount (ml)
Sinapultide	0.862 mg
DPPC	22.50 mg
POPG, Na	7.50 mg
PA	4.05 mg

Note: Amounts reflect reconstituted product at 30 mg TPL/mL

6.2.2 Aerosol characteristics

The emitted dose of the aerosol generated by the ADS is approximately 12.6 mg TPL/min. The mass median aerodynamic diameter (MMAD) of the aerosol is below 5.0 μm, which is considered an appropriate size to be deposited in the alveolus following inhalation. The carrier gas that carries the aerosol to the subject (typically a mixture of air and supplemental oxygen) has a nominal flow rate of 3 L/minute. A disposable fluid trap collects aerosol that condenses within the delivery tubing. Calculations for the theoretical maximum inhaled dose are given in Section 3.2.3.2. The specification for the aerosol temperature at the patient interface is 29 to 41 degrees C.

6.2.3 Packaging and Labeling

Lyophilized lucinactant is supplied in 30-ml glass vials packaged in cartons with foam inserts.

Lyophilized lucinactant and the ADS will be appropriately labeled with the investigational caution statements required by the regional health authority (eg, FDA, EMA) to ensure that users are aware that the product is limited by law to investigational use only.

6.3 Precautions for Aerosol Delivery and Device Usage

The ADS, disposables and study drug are investigational materials which are to be used only for investigational studies with lucinactant for inhalation and not any other purpose. All equipment and supplies are to be returned to Windtree or otherwise destroyed at the end of the study.

Sites must maintain accurate records and proper storage of all delivered and dispensed study drug vials and device components (including the ADS cartridges). Details on study supply accountability and storage are provided in Section 6.9, the study manual, the pharmacy manual, and in the ADS Operator's Manual.

6.3.1 Precautions for Aerosol Delivery

The nCPAP device used during aerosol delivery must be a continuous flow device and have a patient interface, both of which are commercially available for nCPAP delivery to neonates. An unmasked study-trained site designee (eg, respiratory therapist or nurse) must provide close monitoring of the subject and study device during aerosol delivery.

Local NICU policies and procedures for nCPAP delivery are to be used, regardless of treatment group assignment. During study treatment delivery, clinical staff must ensure that the desired level of nCPAP is maintained. Typical maneuvers to improve the delivery of nCPAP (eg, placing an oro- or nasogastric tube, securely but gently immobilizing the subject's head, using pacifiers and/or chin strap), are encouraged during dosing. Subjects must be closely monitored for complications related to placement of the patient interface (see Section 9).

6.3.2 Precautions for Device Usage

Lucinactant for inhalation should be administered only by study staff that are trained on the study protocol, associated procedures on the administration of lucinactant for inhalation, and the subsequent care and monitoring of infants following aerosol exposure. Study personnel must complete all required study training and all local and regional NICU requirements for the operation of an investigational NICU device must be followed. Study infants must be under continuous, close monitoring by trained personnel during and after treatment.

If at any point during set-up, aerosol administration, or at finalization of aerosol delivery, an error screen or audible alarm is generated by the device that may signal a delivery malfunction, the user should follow the on-screen instructions. In most cases, this should resolve the issue and permit users to continue. However, if they are unable to resolve the issue, they must contact previously identified Windtree representative for further instructions (Section 9.3.1). The communication plan included in the study manual will identify users authorized to assist with device problems. In such cases, all local institutional procedures must be followed to ensure continued safety and observation of the subject. The ADS Operator's Manual outlines audible alarms and visual displays that may indicate delivery failure.

If at any time during treatment the safety of the study subject is in question, lucinactant for inhalation must be discontinued, the device must be disconnected and removed from the subject immediately, and local NICU procedures must followed to ensure the care and safety of the subject. Interventions such as endotracheal intubation, mechanical ventilation, and commercial surfactant administration must be readily available for all study infants being administered lucinactant for inhalation.

6.4 Description of Treatment Groups

The study treatment, 'lucinactant for inhalation,' consists of the investigational drug, reconstituted lucinactant and the ADS. The rationale for the selected device and study treatments, including active and control, is discussed in Section 3.2.

6.4.1 Aerosol Delivery in the Active Treatment Groups

Randomization must occur within 6 hours of birth. Study treatment with lucinactant for inhalation must be initiated as soon as possible (within 2 hours of randomization), but no later than 8 hours after birth. For the first 2 subjects at each site and subjects randomized to the active study treatment group, the duration of the initial treatment is 100 minutes (corresponding to 160 mg TPL/kg). The subject will be connected to the study nCPAP and study airway connector (see Section 8.7.3). Following this change in the airway circuit, subjects will need to stabilize for at least 15 minutes before being connected to the ADS.

Subjects are eligible to receive up to 3 repeat treatments (a total of 4 treatments) of the treatment to which they are originally assigned; however, repeat doses for the active treatment will be 80 mg TPL/kg. Repeat treatments will be given as soon as 20 minutes from completion of the previous treatments up to 36 hours after completion of randomization if the subjects meet repeat treatment criteria (Section 6.6). However, all subjects are to receive a repeat treatment, unless the subject is on an FiO_2 of 0.21 (room air) at the end of study treatment dosing (ie, 50 minutes after initiation). Repeat treatments will not be given if it is unsafe to do so in the judgment of the PI.

Preparations for a repeat treatment should begin at the end of the study treatment (eg, reconstituted drug product requested from pharmacy). If a subject is above room air at 100 minutes (or 50 minutes for repeat dosing) after initiation but subsequently is at room air at the time the repeat treatment is ready to be delivered, the dosing team may elect to not deliver the repeat dose. If study drug was reconstituted but not used, it may be used (treatment initiated) up to 5 hours after reconstitution if the subject requalifies within this time. Note that the reconstituted product may only be given to the subject to which it was assigned; it cannot be used for another subject.

The PI will follow routine practice guidelines to determine when a subject in either treatment group requires rescue surfactant therapy or escalation of respiratory support. All study treatments are masked (see Section 6.6).

6.4.2 Control ("Sham") Treatment in the Control Group

As described in Section 3.2.2, no inert placebo exists. The optimal control, therefore, is to simulate study drug treatment in a masked fashion by bringing the ADS to the bedside but not administering any study drug, a procedure known as "sham" treatment.

For sham treatment, no active drug will be prepared. Instead, the ADS will be prepared and delivered to the bedside in a masked manner. Masking will occur as with active treatment (eg, behind a curtain). The subject will be connected to the same setup as active subjects (using the study nCPAP and study airway connector; see Section 8.7.3). Following completion of the setup, subjects will need to stabilize for at least 15 minutes. Subjects receiving sham will simulate being connected to nCPAP via the ADS but the ADS itself will not be powered on or connected. The start time for sham treatment (treatment initiation) will be the time at which this simulated connection occurs; the stop time will be 110 minutes later (to account for an approximate 10 minutes to switch the syringe and cartridge in the active treatment group). The subject will remain masked for the same duration as active subjects. As with the active treatment, if the subject's FiO_2 level is not at room air (0.21) by the end of the "treatment" time, the site should prepare and conduct a repeat "treatment"; each repeat treatment time will be 50 minutes. At the end of the assigned sham treatment time, the subject will be switched to clean nCPAP equipment (if necessary), as occurs at the end of active treatment. Masking equipment may then be removed.

As with active treatment, control/sham treatment is to begin within 2 hours after randomization. Repeat control/sham treatments (up to 3) are to be given if repeat treatment criteria are met, unless it is unsafe to do so in the judgment of the investigator (see Section 6.6). As described in Section 3.2.2, repeat treatment with control/sham in subjects who do not require intubation is ethical.

6.5 Treatment Groups and Method of Treatment Group Assignment

Subjects will be assigned to receive either 160 mg TPL/kg lucinactant for inhalation in conjunction with nCPAP or control (sham treatment).

Table 6-2. Study Assignments by Treatment Groups

Treatment Group	Study Assignment
160 mg/kg	160 mg TPL/kg of lucinactant for inhalation, delivered as two consecutive 50-minute administrations, in conjunction with nCPAP (n ≈ 65) Up to 3 repeat study treatments of lucinactant for inhalation 80 mg TPL/kg are to be given if repeat treatment criteria are met
Control	Continuous nCPAP with sham drug treatment for 110 minutes (n ≈ 65) Up to 3 repeats of 50-minute sham treatments are to be given if repeat treatment criteria are met.

Note: The first 2 subjects at each site will receive open-label active treatment. Masking procedures for the initial treatment will be followed for all repeat treatments in all treatment groups

Preterm neonates who successfully meet all eligibility criteria will be randomly assigned within their applicable stratum (26 to 28 completed weeks PMA or 29 to 32 completed weeks PMA) to one of the 2 treatment groups in a 1:1 ratio. Subjects will be randomized/enrolled using centralized allocation electronically (eg, interactive response technology [IRT]), including the open-label subjects (the first 2 subjects at each site). Neonates from multiple births will be randomized independently. Randomization information will be provided to the study drug preparer (eg, pharmacist). The PI, study staff (eg, site coordinator) (as applicable), and attending physicians as appropriate will be masked to the treatment assignment, as described in the site's blinding/masking plan. Infants who are randomized and on study nCPAP but no longer meet qualification criteria before treatment will still receive the study treatment, unless it is unsafe to do so in the opinion of the investigator.

6.6 Repeat Treatments

Up to 3 repeat treatments will be administered to each subject, regardless of treatment group assignment, up to 36 hours following randomization. For each subject, repeat treatments will occur if repeat treatment criteria are met, unless it is unsafe to do so in the judgment of the investigator. It is required that all subjects receive a repeat treatment after the previous treatment, unless the subject is on an FiO_2 of 0.21 (room air). Masking procedures used for the initial treatment will be followed for repeat treatments (see Section 6.7).

The repeat treatment criteria are defined as follows:

- Time: ≥ 20 minutes from completion of the previous treatment (up to 36 hours following randomization)
- Respiratory support: Subject has a need for $FiO_2 > 0.21$ to maintain SpO_2 of 90% to 95%.

The repeat treatment should occur as soon as possible after the 20-minute time period has elapsed, but no more than 1 hour after meeting criteria.

As with the initial treatment, the randomization/inventory system will be used to receive the drug kit assignments, and all other procedures that were performed for the initial treatment will be followed for the administration of the repeat treatments.

6.7 Study Masking

In order to minimize bias in subject assessments, study treatment masking (blinding) will be employed. Details of the masking procedure are provided in the 03-CL-1702 Overall Blinding Plan, Blinding Procedure, Blinding Maintenance and Assurance Plan, and Statistical Analysis Plan documents. The blinding plan is outlined as follows:

a. In all circumstances, subject safety takes precedence over maintenance of study masking. If at any point masking equipment interferes with emergent patient care or knowledge of study treatment is required for patient management, then the blind should be broken. If this occurs, Windtree must be notified as soon as possible (see Section 9.3.2).

b. Personnel making or influencing clinical decisions – especially regarding intubation or the level of respiratory support – must be masked from treatment assignment. Every effort should be made to maintain study masking at all times unless the blind needs to be broken for reasons of subject safety. Clinicians may be masked for different subjects at different times, depending on the logistics at each site.

c. As there are potentially many ways in which treatment assignment might be masked, each site will create a site-specific blinding plan to be followed throughout the study that specifies which staff members (or types of staff members) are masked and which are not, and at what times. This blinding plan must be approved by Windtree prior to subject recruitment.

d. Operational requirements of blinding are described in the Blinding Procedure document. Generally, active or sham drug syringes and materials will be prepared by an unmasked drug preparer at the time dosing is required and will be obscured from view when

transported to the bedside with the ADS. Once at the bedside, visual barriers will be put in place to block dosing equipment from view outside the immediate bedside area. An unmasked dosing team will then administer active study drug or sham drug treatment. The start time (treatment initiation) for sham will be the time at which the sham setup is complete and the nCPAP circuit is interrupted (to simulate connection to the ADS); the stop time will be 110 minutes later for the initial treatment.

e. As the ADS is virtually silent, no auditory blinding devices are required (eg, "white-noise" generator). At the conclusion of treatment, unless a repeat treatment is immediately warranted, the dosing team will replace any visibly soiled nCPAP equipment, break down the dosing equipment, remove all residual active drug from the subject, remove the visual barriers, and transport the waste (obscured from view) for disposal, and the ADS back to storage.

6.8 Early Discontinuation of Study Treatment

The administration of study treatment may be discontinued at any time prior to the completion of dosing if certain device error codes occur which cannot be corrected in a safe and timely manner or based on the clinical judgment of the PI. Reasons for discontinuation of study treatment include, but are not limited to the following:

1. Device failure or malfunction occurs. If device failure or malfunction occurs, the user should follow the on-screen instructions to resolve the issue. If they are unable to resolve the issue, they must contact the previously-identified Windtree representative for further instructions (Section 9.2).
2. Automatic treatment interruption due to a pre-defined condition (eg, syringe high pressure error). If automatic shutdown occurs, Windtree personnel should be contacted as soon as possible (per Section 9.2).
3. An AE or ADE which places subject safety at risk (eg, pulmonary hemorrhage, airway obstruction).
4. If, in the PI's best medical judgment, continuing the subject's exposure to study treatment is not in the best interest of the subject's safety.

5. Signs of acute respiratory deterioration develop, as evidenced by a clinically significant increase in respiratory rate or effort (work of breathing) plus at least one of the following:
    a. A persistent (at least 10 minutes) $FiO_2 \geq 0.70$ or a sustained increase from baseline by ≥ 0.30 to maintain SpO_2 90% to 95%
    b. A persistent (at least 5 minutes) transcutaneous $PCO_2 > 70$ mm Hg or an increase from baseline by ≥ 20 mm Hg
    c. Recurring episodes of bradycardia
    d. A sustained apneic event (≥ 20 seconds)

Subjects whose treatment is discontinued based on the PI's judgment will continue in the study. Subjects whose treatment is discontinued based on the parent/guardian's withdrawal of consent must be withdrawn from the study and no further data collection will be done.

In accordance with local institutional practices, an approved SRT must be made available to subjects demonstrating a clinical need if dosing is discontinued early.

6.9 Clinical Study Supplies at the Clinical Study Site

6.9.1 Investigational Study Drug and Disposable Device Components

Lyophilized lucinactant and disposable device components (eg, syringes, cartridges) will be shipped either to the investigational clinical study site pharmacy or to a designated location at the clinical study site. Study sites must verify each shipment via the study IRT, and report study drug shipping temperatures to Windtree as outlined in the study manual.

6.9.2 Ancillary Supplies

Ancillary supplies (eg, nCPAP system, nasal prongs) will be shipped either to the investigational clinical study site NICU or to a designated location at the clinical study site. Study sites must verify each shipment to Windtree via the Clinical Supply Receipt Form that accompanies the shipment.

6.9.3 Dispensing

Study supplies (study drug, cartridges, related study equipment) will be dispensed in accordance with the subject's randomized treatment group (Section 6.5). The NICU pharmacist or designated study personnel will provide on-site storage, dispensing, reconciliation, and documentation of study supplies as outlined in the study manual. Study drug and device disposables must be fully reconciled at the end of the study. The unblinded study clinical site monitor will provide oversight

of these tasks and communicate any significant findings or indications of noncompliance to Windtree.

6.9.4 Storage of Lucinactant and AEROSURF Delivery System

Lyophilized lucinactant must be stored in a secured area of the hospital pharmacy or NICU at 2°C to 8°C and protected from light until use. The refrigerated storage should have an alarm for out of range temperatures. Study sites must monitor and log storage temperatures daily. All temperature excursions should be reported to Windtree as outlined in the study manual (see also Section 9.2).

The ADS will be delivered separately and must also be stored in a secure location under the recommended storage conditions outlined in the ADS Operator's Manual.

6.10 Study Compliance

Study compliance to treatment administration will be based on the timing and duration of actual study treatment delivered in comparison to the expected timing and duration based on the study treatment to which each subject was randomized. Aerosolization time and duration will be tracked by the ADS, which will display a continual count of lucinactant exposure time throughout the aerosol delivery period. Duration of sham treatment will be 110 minutes for the initial treatment and 50 minutes for repeat treatments. The duration of lucinactant exposure or sham treatment will be documented in the study eCRF.

The number of subjects randomized but not treated, and the number of subjects whose study treatment is discontinued early will be recorded in the eCRF and summarized in the study report.

6.11 Study Drug and Device Accountability

It is the responsibility of the PI and designee to ensure that all study supplies (vials of lucinactant for inhalation, all components of the ADS, related equipment) are inventoried and appropriately stored in accordance with study guidance documents (eg, study protocol, ADS Operator's Manual, study manual), and used only for study subjects, by trained staff.

6.11.1 Study Supply Accountability

The following guidelines must be followed to ensure the storage and accountability of the study supplies is consistent with the study protocol:

1. Used or partially used vials of lucinactant for inhalation and disposable device components must be kept separate from unused supplies throughout the life of the study.

2. Designated study personnel will return all unused study drug vials to the pharmacy or the clinical supply storage area immediately after the completion of study treatment.
3. Reconciliation of study supplies will be performed at each study visit by the unblinded clinical site monitor and recorded appropriately in the pharmacy log and drug and device accountability records. Following reconciliation, study supplies will be destroyed and/or returned.
4. Storage conditions, as described in the study manual, will be assessed and documented by the unblinded clinical site monitor at each study visit (ensuring all supplies are kept in a secure area with restricted access).
5. Dispensing information must be recorded on the inventory log and kept with the study site records in the pharmacy binder throughout the study.
6. Study sites will not dispense the study supplies to any personnel other than those listed on Form FDA 1572 - Statement of Investigator, or on the Signature and Delegation Log.

7 DATA MONITORING COMMITTEE

The purpose of the data monitoring committee (DMC) is to evaluate the degree of risk involved in study subject participation within each treatment group and to determine if study continuation in accordance with the current protocol holds the potential to institute any undue harm or threat to the safety and welfare of study subjects. During the primary phase (screening to 36 weeks PMA), the chair of the DMC will receive regular reports on SAEs and AEs of interest (see Section 9.1) and DMC members will be updated on the program and trial status twice a year (outside of formal meetings) at spring and winter neonatology national meetings. In addition, there will be one planned meeting during study conduct, when enrollment is approximately 1/3 of the total enrollment of 70 (ie, approximately 28 subjects). An ad hoc meeting of the DMC will occur if the chair deems it necessary to address safety in the study. The DMC may recommend that study enrollment be suspended if safety concerns are identified or suspected.

The DMC will also convene meetings after all subjects have completed 36 weeks PMA and 12 months follow-up.

The DMC will consist of 3 to 5 experts in the field of RDS; at least 2 of the experts must be neonatologists.

7.1 Safety Reviews

A DMC review may consist of the evaluation of (1) all AEs, (2) ADEs relevant to potential subject safety issues, (3) case reviews of subjects with reported SAEs, and (4) summary tables of all safety endpoints (Section 4.4).

Following a meeting, the DMC will provide timely recommendations to the Windtree study team. Recommendations may consist of, but not be limited to the following:

- Continue the study as planned
- Suspend study enrollment, pending additional information
- Close study enrollment

An unmasked independent statistician, not a member of the committee, will be responsible for the statistical analysis of the data.

8 STUDY PROCEDURES AND GUIDELINES

A table of study procedures and activities is presented in Section 1.2.

Before conducting any study-related activities, a signed written ICF must be signed and dated by the subject's legally authorized representative (Section 12.2).

8.1 Vital Signs and Gas Exchange Parameters

8.1.1 Vital Signs

Vital signs (body temperature, respiratory rate, and heart rate) will be documented at randomization (± 5 minutes) and every 30 (± 5) minutes until study treatment initiation (active or sham).

Vital signs will be recorded:

- Study Days 1-3: time 0 (T_0; study treatment initiation), 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150 minutes (± 3 minutes) after initiation; 3 ± 0.5, 6 ± 1, 9 ± 1, 12 ± 1, 18 ± 2, 24 ± 2, 36 ± 2, 48 ± 2, 60 ± 2 and 72 ± 2 hours after initiation.
- Repeat study treatments: treatment initiation, 10, 20, 30, 40, 50, 60, 70 minutes (± 3 minutes) after initiation.
- Study Days 4-7: daily at 0800 and 2000 hours (± 2 hours)

During study treatment administration, except T_0, temperatures will not be recorded. If timing for measurements overlap, only one measurement should be taken.

8.1.2 Gas Exchange Parameters

Oxygen (O_2) saturation for each subject will be monitored by pulse oximetry (SpO_2); PCO_2 will be assessed for each subject by a transcutaneous monitor (eg, SenTec). Values for gas exchange parameters (PCO_2, FiO_2, SpO_2) and PEEP will be documented at randomization (± 5 minutes) and every 30 minutes following randomization until study treatment initiation (active or sham). The transcutaneous monitor must be calibrated for accuracy against a blood gas value (arterial, capillary, or venous) at the time of initial set-up and recalibrated, as necessary, in accordance with local institutional practices to ensure accuracy of the monitor output.

Gas exchange parameters will be recorded:

- Study Days 1-3: time 0 (T_0; study treatment initiation), 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150 minutes (± 3 minutes) after initiation; 3 ± 0.5, 6 ± 1, 9 ± 1, 12 ± 1, 18 ± 2, 24 ± 2, 36 ± 2, 48 ± 2, 60 ± 2 and 72 ± 2 hours after initiation.
- Repeat study treatments: treatment initiation, 10, 20, 30, 40, 50, 60, 70 minutes (± 3 minutes) after initiation.
- Study Days 4-7 for FiO_2 and SpO_2: daily at 0800 and 2000 hours (± 2 hours).
- Final Visit: FiO_2

If timing for measurements overlap, only one measurement should be taken.

8.2 Physical Examination

A complete physical examination will be performed by the PI or designee. The designee must be a member of the site-based staff qualified to performed physical exams (such as a nurse practitioner or physician assistant); physical examinations performed at screening must be reviewed and approved by the PI. Any new, clinically significant abnormal physical examination findings at the final period must be documented as AEs in the eCRF.

At the one-year corrected age follow-up, an abbreviated physical exam should be performed and recorded in the eCRF.

8.3 Chest Radiograph

A chest radiograph for the diagnosis of RDS and exclusion of air leak may be performed to assist in the screening assessment but is not required. However, a chest radiograph is required prior to dosing to confirm the diagnosis of RDS and to rule out other conditions. A radiograph obtained in the course of clinical management may be used in lieu of obtaining samples specifically for this study. A blinded review of all radiographs may be performed by Windtree or designee.

A chest radiograph will be required for study subjects who are intubated for any indication during the first 7 study days, if the procedure does not delay or compromise the emergent care of the subject.

8.4 Demographics

Demographic information (gestational age, sex, race, ethnicity) will be recorded at screening.

8.5 Maternal, Birth, and Medical History

The subject's relevant medical information will be recorded at screening, including the following:

- Maternal history, including rupture of membranes (time relative to birth, type), presence of clinical chorioamnionitis, use of antenatal steroids (number of doses)
- Birth history, including date and time of birth, mode of delivery (vaginal, Caesarian section), single or multiple birth (number), Apgar score (assessed at 1 and 5 minutes of life), presence of congenital anomalies, birth weight in grams, use of sustained inflation resuscitation technique
- Medical history, from birth to randomization

8.6 Concomitant Medications

Concomitant medications and therapies required for the general care of the subject are permitted, except for investigational agents, investigational medical devices, or any SRT before randomization (see also Section 8.6.1).

All concomitant medication and concurrent therapies will be documented from birth until the time the subject completes the primary phase of the study (36 weeks PMA), is discharged from the hospital, dies, or is transferred to another hospital (Section 10.2). Dose, route, unit, frequency of administration, indication for administration, and dates of medication will be captured on the eCRF.

For the long-term follow-up period, information on bronchodilators, steroids, and palivizumab (Synagis®; MedImmune, LLC, Gaithersburg, MD, USA) will be collected.

8.6.1 Use of Additional Surfactant Replacement Therapies

Following randomization, commercially available SRT may be administered to subjects whose respiratory status has deteriorated such that conventional SRT is in the subject's best medical interest in the judgment of the investigator (ie, "rescue surfactant"). Because conventional SRT requires endotracheal intubation (even if a tube other than an endotracheal tube is used, such as a thin catheter), subjects receiving commercially available SRT will be considered intubated and to have respiratory failure due to RDS (see Section 4.3.1). Such subjects remain in the study and are followed until study completion but will not receive study treatment.

8.6.2 Use of Caffeine Citrate or Systemic Corticosteroids

Use of caffeine citrate or other methylxanthines is recommended and will be recorded as with any other concomitant medication.

Use of prenatal steroids is permitted. Postnatal steroids are not permitted unless a clear medical need is determined.

8.7 Respiratory Support and Oxygen Delivery

8.7.1 General Principles for Respiratory Support

For the purposes of this study, nCPAP refers to any device which maintains a constant airway pressure above ambient pressure and uses a patient interface on the subject's face (eg, nasal prongs, mask). Non-invasive ventilation (NIV) refers to any device which generates a constant or variable positive pressure and uses a patient interface on the subject's face (see also Section 8.7.4). Therefore, nCPAP is a form of NIV with a constant airway pressure, while SiPAP, non-invasive positive pressure ventilation (NIPPV) and IPPB would be examples of NIV with variable pressures. The study nCPAP device is the specific bubble nCPAP device and interface supplied by Windtree for use with the ADS.

MV refers to any device which generates a constant or variable positive pressure via an endotracheal tube or tracheostomy. For this study, MV using a non-invasive interface will be considered non-invasive ventilation. Oxygen-only support refers to delivery of oxygen without the generation of pressure above ambient pressure (eg, standard-flow nasal cannula).

Study subjects are to be maintained on study nCPAP from the time of randomization until at least 6 hours after they have completed delivery of either treatment as outlined in Section 8.7.3. The management of respiratory support (including nCPAP) and oxygen delivery is otherwise at the discretion of the study PI, keeping in mind that repeat treatments of lucinactant for inhalation can be delivered only on study bubble nCPAP.

The study definition of respiratory failure due to RDS (Section 4.3.1) is used for categorization and analysis purposes only; it is not intended to mandate or guide clinical decision making.

8.7.2 Emergent Respiratory Support

Emergent endotracheal intubation and MV, in accordance with local institutional guidance, must be initiated at any time if deemed necessary for subject safety. Masking may be broken, if necessary, for subject safety.

Any clinical event indicating a need for MV, additional ventilatory support, or increases in oxygen must be evaluated as a potential AE (Section 8). If it is determined that the event qualifies as an AE, it must be reported in the study eCRF as such.

8.7.3 Use of Nasal Continuous Positive Airway Pressure

Study treatment may be delivered only via the study interface and nCPAP device, known as "bubble nCPAP." Subjects are to remain on study nCPAP for at least 6 hours following each study treatment; 24 hours is strongly recommended, and ideally the subject will remain on study nCPAP until 36 hours following randomization (when re-dosing is no longer permitted). If a subject is switched from study nCPAP to an alternate form of NIV within 6 hours of dosing, the reason will be documented in the eCRF.

Changing to an alternate form of nCPAP or other form of NIV in absence of escalating respiratory support requirements may on occasion be necessary but is discouraged for a number of reasons. First, there are currently no definitive data to support that any form of NIV produces superior outcomes to any other form when used as a primary support modality. Second, each change in modality results in transient removal of positive airway pressure from the subject, which may cause alveolar derecruitment and subsequent respiratory deterioration, thereby presenting a safety risk. Third, use of modalities other than study nCPAP may pose a disincentive to administer repeat treatments, since to do so would require changing back to study nCPAP, which carries the risk of derecruitment as described, as well as additional logistical burden.

The study nCPAP device and patient interface is commercially available and FDA-registered. On-site study and clinical staff will be trained by Windtree (or a qualified designee) on the use of the study nCPAP and interface. All local institutional policies and procedures relevant to the administration and safety surveillance of nCPAP must be followed in conjunction with study specified procedures and assessments and in accordance with good clinical practice and judgment. During the nCPAP delivery, subjects must be monitored for complications related to placement of the patient interface.

Procedures that may optimize nCPAP delivery include ensuring proper placement of the patient interface, inserting an oro- or nasogastric tube, maintaining the subject's neck position in a mild extension that is comfortable for the subject, using pacifiers or chin strap, and suctioning the mouth and nose as needed.

Initial nCPAP settings will depend on the subject's clinical condition. Should the subject require increased respiratory support, incremental increases in FiO_2 (to a maximum of 0.45) or nCPAP

should be made by 1 cm H_2O until a maximum nCPAP of 8 cm H_2O is achieved. If a sustained nCPAP of > 8 cm H_2O or $FiO_2 \geq 0.45$ are necessary to maintain an SpO_2 of 90% to 95% or if $PCO_2 > 50$ mmHg, then other forms of respiratory support may be employed. If unsuccessful, the subject should be evaluated for clinical signs and symptoms consistent with respiratory failure due to RDS (Section 4.3.1) and treated accordingly.

8.7.4 Use of Non-Invasive Ventilation

In subjects eligible for this study, NIV must be implemented within 30 minutes of birth. In the delivery room, intermittent positive pressure breaths may be administered manually or mechanically through a non-invasive patient interface (eg, mask or nasal prongs) for no longer than 10 minutes. Following delivery, any mode of NIV or non-invasive oxygen support may be used to support respirations as clinically indicated. However, if part of the unit's standard of care, it is strongly recommended that potential subjects are initiated with bubble nCPAP to minimize the number of changes and time to treatment should the infant qualify for the study.

Subjects are eligible for screening if any form of non-invasive support is instituted within 30 minutes of birth and the investigator feels it is safe to switch the subject to study nCPAP (or if the subject is already on nCPAP). After informed consent is obtained, subjects not already on study nCPAP should be switched to study nCPAP/interface for screening. If, within the first 6 hours after birth, the subject is stable for ≥ 15 minutes on study nCPAP of 5 to 7 cm H_2O with an $FiO_2 \geq 0.25$ to 0.35 to maintain an SpO_2 of 90% to 95% and meets all other inclusion/exclusion criteria, that subject may be enrolled.

8.7.5 Documentation of Respiratory Support Parameters

8.7.5.1 Documentation during the Primary and Extended Periods

From the time of randomization until completion of Study Day 7, respiratory support parameters must be documented in the study eCRF. For each intubation and change in respiratory support, the following must be documented:

a. Date and time

b. The type of respiratory support and mode

c. The reason for each intubation and change of respiratory support

8.7.5.2 Documentation during Final Period

From Study Day 8 until the subject completes the study (36 weeks PMA [or 28 days of life, whichever is later], discharged, transferred, or dies, whichever occurs first), the date and time of each intubation and change of respiratory support must be documented in the study eCRF. If the subject is discharged or transferred to another hospital prior to 36 weeks PMA, the time of discharge or transfer will be documented in the study eCRF. If the subject is on respiratory support at the time of discharge or transfer, the type of respiratory support and the mode must be documented in the study eCRF.

8.7.5.3 Documentation during Longer-Term Follow-up Phase

During the longer-term follow-up phase, the total amount of time on each ventilatory support mode, occurrence of respiratory syncytial virus (RSV) infection (as determined by specific Polymerase Chain Reaction [PCR]) and administration of Synagis for the first time must be documented in the study eCRF at 6 (via telephone or report), and 12 months corrected age.

8.8 Technical Performance of the Device

The following parameters will be captured in the eCRF to document the performance of the device:

a. Information from touchscreen display:
    1. Total treatment duration
    2. Total amount dispensed
    3. Number of pauses
    4. Total time paused
b. Issues associated with device tubing (eg, CPAP tubing detachments, aerosol tube detachments, proximal pressure port obstruction, aerosol tube condensate obstruction).
    5. The number of the detachments that are intentional and unintentional will also be recorded
c. Aerosol or study drug (liquid) leakage before the subject interface (eg, disconnect of the inspiratory circuitry).
d. Occurrence of alarm signals before, during, or after treatment.
e. Any automatic system shutdowns with an associated error code.
f. Inability to maintain nCPAP, with a description.
g. ADS temperature alerts (high or low).

8.9 Initial Discharge

The date of the subject's initial discharge from the hospital will be recorded, regardless of when it occurs.

8.10 6 and 12-Month Follow-up

8.10.1 Health Assessment

The subject's overall health and the occurrence of any respiratory diseases since the previous assessment will be recorded at 6- and 12-months corrected age.

8.10.2 Abbreviated Physical and Neurological Exam

An abbreviated physical and neurological exam will occur at 12 months corrected age.

In addition, growth parameters (length, weight, head circumference) will be recorded at 12 months corrected age.

8.10.3 Hospitalizations and Emergency/Urgent Care Visits

The number of hospitalizations and emergency/urgent care visits after the initial discharge, when they occurred, the duration of visits, and the reason will be reported from 36 weeks PMA to the 6- and 12-month corrected age follow-up period visits.

8.11 End of Study Definition

A subject is considered to have completed the study if he or she has completed all phases of the study through initial discharge, including the last scheduled procedure at 36 weeks PMA (or 28 days of life, whichever is later), as shown in the Schedule of Activities (SoA), Section 1.2. It does not include the 6- and 12-month follow-up visits.

The end of the study is defined as completion of the last visit or procedure for the last subject in the trial (last subject/last visit).

9 ADVERSE EVENT REPORTING

Information regarding the occurrence of AEs will be assessed from the time of randomization until completion of 36 weeks PMA/Final Visit. Incidence of ADEs will be assessed from the time of randomization until completion of Study Day 7.

For purposes of this study, the following will be considered AEs of special interest:

1. AEs during the dosing period (ie, peri-dosing events), defined as the following AEs with an onset time ≤ 2 hours from the time of initiating study treatment:

    - Apnea (lack of inspiratory air movement sustained for ≥ 20 seconds and coincident with at least one of the following: SpO_2 < 80%, HR < 100 bpm, requirement for PPV administered manually or mechanically through any patient interface)
    - Bradycardia (heart rate < 100 bpm sustained for ≥ 20 seconds)
    - Desaturation (SpO_2 < 80% sustained for ≥ 20 seconds)
    - Gagging/regurgitation
    - Pallor

2. Complications related to placement of the patient interface as identified by the following:

    - Bleeding
    - Apparent obstruction of the nares
    - Occlusion of the interface requiring removal and replacement
    - Nasal irritation (erythema of nares or septum, inflammation of nares or septum)

3. Air leak is considered an AE of special interest if it occurs at any time during the study. Examples of air leak include the following:

    - Pneumothorax
    - PIE
    - Pneumomediastinum
    - Pneumopericardium
    - Subcutaneous emphysema

Complications of prematurity, including IVH, PVL, pulmonary hemorrhage, apnea, NEC, PDA, acquired sepsis, and ROP, will be summarized but are not considered AEs of special interest.

9.1 Adverse Events

An AE is defined as any untoward medical occurrence in a study subject who is administered a pharmaceutical product that does not necessarily have a causal relationship with this product. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product (drug and/or device), whether or not related to the investigational product (see ICH guideline E2A *Clinical Safety Data Management: Definitions and Standards for Expedited Reporting*).

An ADE is an AE directly related to the use of or caused by the investigational device, such as nasal irritation from the nasal prongs. An ADE should not be an event that is associated with study treatment, such as desaturation. ADEs are treated the same as all other AEs. For serious ADEs, see unanticipated adverse device effects (UADE) in Section 9.1.5.

All AEs and ADEs ongoing at the final visit must be followed by the PI until resolution, or for at least 30 days post 36 weeks PMA.

Documentation of AEs in the eCRF must include the following parameters; (1) duration (time of onset and resolution), (2) severity, (3) outcome, (4) action taken, and (5) relationship to study drug and/or device. AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA).

The term “sepsis” (or a variant of that term, such as “clinical sepsis”) will be used if the subject has a diagnosis consistent with sepsis. However, if it is later determined that the subject does not have sepsis, the terms that describe the subject’s symptoms should be used instead, such as “fever” or “leukocytosis”; the terms “rule-out sepsis” or “suspected sepsis” cannot be used.

The standard of care use of nCPAP for respiratory support of preterm neonates include the following inherent risks: excess air in the stomach, redness or irritation of the nose, congestion or runny nose, and pneumothorax. If any of these occur, and the PI determines that it was likely caused by nCPAP, it should be not be considered related or possibly related to the investigational treatment.

9.1.1 Causal Relationship of Adverse Events

The relationship of an AE (and ADE) to a study drug is assessed by the PI or blinded designee using the following definitions:

- Not related: The AE is clearly related to other factors, such as the subject's clinical state, therapeutic interventions, or concomitant drugs.
- Unlikely Related: The AE was most likely produced by other factors, such as the subject's clinical state, therapeutic interventions, or concomitant drugs, and does not follow a known response pattern to the study drug.
- Possibly Related: The AE follows a reasonable sequence from the time of drug administration and/or follows a known response pattern to the study drug, but could have been produced by other factors, such as the subject's clinical state, therapeutic interventions, or concomitant drugs. An AE that is determined to be due to the subject's underlying disease state or is common for this patient population generally should not be considered possibly related.
- Related: The AE follows a reasonable temporal sequence from the time of the drug administration and meets the following criteria;
    a) Follows a known response pattern to the study drug
    b) Cannot be reasonably explained by other factors such as the subject's clinical state, therapeutic interventions, or concomitant drugs
    c) Meets one or more of the following:
        - occurs immediately following study drug administration
        - improves on stopping the drug
        - reappears on repeat exposure
        - there is a positive reaction at the application site

  An AE that is determined to be due to the subject's underlying disease state or is common for this patient population generally should not be considered related.

9.1.2 Severity Grade Levels of Adverse Events

The severity of an AE is assessed by the PI using the following definitions:

- Mild: Events require minimal or no treatment and do not interfere with the subject's daily activities
- Moderate: Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- Severe: Events interrupt a subject's usual activity level and may require systemic drug therapy or other treatment and may be potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious."

9.1.3 Adverse Event Procedures

All AEs (and ADEs) are to be assessed in all subjects throughout the study period (from enrollment to study withdrawal or completion) and documented in the study eCRF. Each AE should be reported spontaneously or in response to general, non-directed discussion with the attending nurse or physician (eg, has there been any change in subject status since the last assessment period?). For each AE, the investigator should obtain all information required to complete the AE page of the eCRF, in accordance with eCRF completion guidelines (provided separately by Windtree).

All AEs, regardless of seriousness, severity, or relationship to study participation, must be recorded (using medical terminology) in the source document and on the AE page of the eCRF. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology.

All AEs must be followed until resolution or until a stable clinical end-point is reached, or for at least 30 days after the subject's last day in the study if an AE is ongoing at the time the subject completes the study. All measures required for AE management and the ultimate outcome of the AE must be recorded in the source document and reported on the AE page of the eCRF.

9.1.4 Serious Adverse Events

An SAE is any untoward medical occurrence that meets one of the following criteria (ICH E2A, *Clinical Safety Data Management: Definitions and Standards for Expedited Reporting*):

1. Results in death
2. Is life-threatening
3. Requires inpatient hospitalization or prolongation of existing hospitalization
4. Results in persistent or significant disability/incapacity
5. Is a congenital anomaly/birth defect
6. May be considered serious when based upon appropriate medical judgment

When the investigator or trained designee becomes aware of an SAE, Windtree must be notified as soon as possible (and no later than 24 hours after the event has occurred) via telephone or email, regardless of the relationship (or lack thereof) of the SAE to study participation.

SAEs can be reported to the Windtree SAE reporting line (see Study Manual). In addition, all SAEs will be reported to the President of the Office for Registration of Medicinal Products, Medical Devices, and Biocidal Products in Poland in a timely manner, in particular, in accordance to the article #51 of the act about medical products dated 20 May 2010.

When reporting SAEs, the following information should be provided:

1. Study identifier
2. Study center
3. Subject number
4. A description of the event
5. Date of onset
6. Current status
7. Clarification on whether study aerosol was discontinued
8. The reason why the event is classified as serious
9. The Investigator's assessment of the association between the event and study participation

All reports of SAEs must be followed up within 24 hours (or sooner at the request of the medical monitor) by the completion of the SAE form and signature by the person who completed the form and the PI.

In accordance with Windtree's standard operating procedures (SOPs) and regulatory agency (eg, FDA) regulations, investigators will be notified of the occurrence of serious, unexpected, related AEs. The PI must promptly inform the relevant IRB/IEC in accordance with ICH E6 of all AEs that are deemed related to study participation (ie, there is a reasonable possibility that the AE may have been caused by the drug or device) and are thus deemed a significant new AE or risks with respect to the drug or device.

9.1.5 Unanticipated Adverse Device Effects

An UADE is defined as any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigator's brochure, or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

In such cases, Windtree must be notified as soon as possible (and no later than 24 hours after the event has occurred) through the following procedures):

- Contact the unblinded clinical site monitor or designated contact person regarding the event.
- Complete all device reporting procedures detailed in the study manual.

9.2 Safety Reporting

Safety report distribution is the responsibility of Windtree or designee (ie, CRO), which coordinates distribution of safety reports to applicable regulatory authorities and ECs. Finalized

safety reports are distributed by one or more individuals, "Responsible Team," within a department that has responsibility to coordinate the distribution/submission activities, either directly or via a Local Submitting Party on behalf of Windtree.

The Responsible Team receives finalized safety reports (eg, CIOMS-I form/MedWatch 3500A/ E2B file/DSUR/SUSAR Listing/PSUR/PADER) and coordinates distribution to all applicable regulatory authorities and ECs. Distribution will be done in accordance with project-specific documents, regulatory requirements, other applicable reference sources (eg, Clinical Trial Management System [CTMS] output), and applicable Windtree or designee safety procedural documents.

In addition, Windtree coordinates translation when required for safety reporting. Windtree also coordinates transcription (eg, manual transfer of information from one reporting format to another) when required. Project specific information is used to identify appropriate recipients. Quality checks will be permed on the distribution documents and recipient information for completeness and accuracy prior to distribution.

9.3 Windtree Contact Information

The names, telephone, and email numbers of the individuals who should be contacted regarding trial-related questions and safety are listed below and are provided in the communication plan included in the study manual.

9.3.1 Trial-Related Questions

For trial-related questions, such as study conduct, please call your clinical site monitor. For device- and drug-related issues, please refer to the communication plan.

9.3.2 Medical Monitoring

FOR MEDICAL QUESTIONS, PLEASE CONTACT THE MEDICAL MONITOR:

Steven G. Simonson, MD (Medical Monitor)
Office: + 1 (215) 488-9474
Mobile: +1 (267) 454-4931
Email: SSimonson@Windtreetx.com

or

Carlos Guardia, MD (Medical Monitor)
WhatsApp: +56 9 4203 9028
Office: +1 (717) 300 1415
Email: CGuardia@Windtreetx.com

or

Robert Segal, MD, FACP (Safety Monitor)
Office: + 1 (215) 488-9450
Mobile: +1 (267) 237-7576
Email: RSegal@Windtreetx.com

FOR SERIOUS ADVERSE EVENTS OR UNANTICIPATED ADVERSE DEVICE EFFECTS, PLEASE CONTACT WINDTREE (see Study Manual)

FOR ADDITIONAL ASSISTANCE, PLEASE CONTACT THE CLINICAL SITE MONITOR OR YOUR ASSIGNED R&D SPECIALIST

10 DISCONTINUATION AND REPLACEMENT OF SUBJECTS

10.1 Early Discontinuation of Study Treatment

The administration of lucinactant for inhalation may be discontinued at any time prior to the completion of dosing based on certain criteria (Section 6.8) or the clinical judgment of the PI. Subjects whose treatment is discontinued based on the PI's judgment will continue in the study. Subjects whose treatment is discontinued based on the parent/guardian's wishes must be withdrawn from the study.

10.2 Withdrawal of a Subject from the Study

A subject may withdraw consent (through their legally authorized representative) at any time without prejudice to further care.

If a subject is discharged or transferred to another hospital before 36 weeks PMA, the clinical status, including presence or absence of BPD at 36 weeks PMA, should be obtained. If, for any reason, the status of a subject is unknown (eg, subject is discharged home), every effort must be made to contact the subject's legally authorized representative to determine the status of the subject, including phone calls and certified letter(s). If the status of the subject has not been established in 28 days after the subject reaches 36 weeks PMA, the subject will be considered lost to follow-up. Note: All attempts should be made to ensure that no subjects are lost to follow-up.

10.3 Termination of the Study

The study may be terminated prematurely due to safety reasons by the DMC (Section 7).

Additional reasons for study termination include, but are not limited to, the following:

- The local or national regulatory agency requests a termination of the study.
- It has been determined that the risk level associated with the experimental drug is significant and warrants termination of the study.
- Windtree, for reasons other than safety, may terminate the study at any time by written notice of intended termination provided at least 30 days before termination.
- The PI or IRB/IEC, for reasons other than safety, may terminate participation of this clinical site in the study by written notice of intended termination provided at least 30 days before termination.

- Any other clause described in the individual site Clinical Study Agreement (eg, if ICH GCP guidelines or other regulatory procedures are not followed or if enrollment rate is not sufficient to meet study goals).

10.4 Replacement of Subjects

Subjects who discontinue treatment early or who are withdrawn from the study will not be replaced, unless required by the DMC.

11 PROTOCOL VIOLATIONS/DEVIATIONS

A protocol deviation occurs when the PI or any other site staff assigned to the study fail to adhere to any protocol requirement. Protocol deviations include collection of information outside a collection window or failure to collect non-critical information.

A protocol violation occurs when the PI fail to adhere to any significant protocol requirement affecting the inclusion, exclusion, subject safety, and primary endpoint criteria. Protocol violations include but are not limited to the following:

- Failure to meet eligibility criteria
- Use of a prohibited concomitant medication (Section 8.6)
- Failure to comply with ICH GCP guidelines

Windtree will determine if a protocol violation will result in withdrawal of a subject, prior to unblinding of the study treatments.

When a protocol violation or deviation occurs, the site monitor will discuss it with the PI. All protocol violations and deviations will be documented and tracked.

12 ETHICS

This study will be conducted according to the United States and ICH regulations and guidelines (21 Code of Federal Regulations [CFR] Part 50, *Protection of Human Subjects,* 21 CFR Part 56, *Institutional Review Boards,* 21 CFR Part 312, *Investigational New Drug Application*, and ICH E6, *Guideline for Good Clinical Practice)* as well as all applicable local, state, and federal regulations and guidelines regarding the conduct of clinical studies. In addition, this study will be conducted in accordance with the ethical principles included in the World Medical Assembly (WMA) Declaration of Helsinki, *Ethical Principles for Medical Research Involving Human Subjects* adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended most recently by the 64th WMA General Assembly, Fortaleza, Brazil, October 2013.

Throughout this section the term "Clinical Investigator" will be defined, in accordance with 21 CFR 54, as any listed or identified PI or subinvestigator who is directly involved in study dosing or evaluation of research subjects. PIs or subinvestigators must be listed on Form FDA 1572, if applicable, and documented as appropriate on the delegation of authority signature log.

12.1 Institutional Review Board/Independent Ethics Committee/Research Ethics Board

The protocol, including any amendments and the ICF, will be submitted to the appropriate IRB/IEC for each study site for approval to conduct the study. Before the initiation of the study at each study site, Windtree must be provided with a copy of the IRB/IEC approval to conduct the study. This approval must refer to the study by exact protocol title and number and should identify the documents reviewed and the date of review.

Protocol and ICF modifications or changes may not be initiated without prior written IRB/IEC approval, except when necessary to eliminate immediate hazards to the study subjects or when the change(s) involves only logistical or administrative aspects of the study. Such modifications will be submitted to the IRB/IEC and written verification that the modification was submitted and subsequently approved should be obtained. A site must receive approval from Windtree on any ICF modification before submission to the IRB/IEC for approval and subsequent implementation at the study site. Protocol modifications (ie, amendments) may only be enacted by Windtree.

The IRB/IEC must be informed of revisions to other study-related documents or study information that was originally submitted for review. Revised study documentation and related informational updates may include but are not limited to the following:

1. Serious and/or unexpected AEs occurring during the study (reported in accordance with the SOPs and policies of the IRB/IEC)
2. Any new study information that may adversely affect subject safety or study conduct
3. Annual study updates or IRB/IEC requests for reassessment of the study
4. Timely communication of significant actions and related findings from the DMC (to include study enrollment holds or expansion, protocol amendments, or early study closure).
5. Notification of major study/site milestones to include study/site closure

12.2 Informed Consent Form of Study Subject

A signed written ICF will be obtained in accordance with the Declaration of Helsinki, ICH GCP, 21 CFR 50 Subpart B, 2 and 21 CFR 56, Subpart A), HIPAA (where applicable), and local regulations.

The PI will prepare the ICF (to include HIPAA authorization [where applicable]) based on an ICF template provided by Windtree. Completed site-based ICFs must be acceptable to Windtree and be approved by the IRB/IEC. The PI will send an IRB/IEC approved copy of the ICF to Windtree for the study file.

The subject's legally authorized guardian will be provided a consent form describing this study and be provided sufficient information to make an informed decision about the subject's participation in this study. The formal permission of a subject's legally authorized guardian, documented on the IRB/IEC-approved consent form (and any other locally required documents), must be obtained before the performance of any study-related activity, including the cessation of any medications or procedures. The consent form must be signed and dated including the time of consent by the subject's legally authorized guardian, the investigator-designated research professional obtaining the consent, and, if applicable, an impartial witness.

Time to treatment is potentially an important factor in the success of non-invasive delivery of surfactant. Because of this and other operational factors, antenatal consent should be obtained where permitted. Assent of the subject will not be sought, since all subjects are neonates and not capable of providing assent.

12.3 Financial Disclosure

The FDA has issued regulations (21 CFR Part 54, *Financial Disclosure by Clinical Investigators*) that require sponsors to submit complete and accurate certification or disclosure statements to certify the absence of certain financial interests of clinical investigators and/or to disclose those financial interests, as required, when clinical studies are submitted to FDA in support of marketing approval. These regulations are intended to ensure that financial interests and arrangements of clinical investigators, that could affect reliability of data submitted to FDA in support of marketing approval, are identified and disclosed by the sponsor.

Clinical investigators will be asked to disclose proprietary (eg, patent, licensing agreement) and financial (eg, stock options, royalty) interests as they pertain to Windtree, before participating in the study. In addition, clinical investigators will be required to consult with Windtree before acquiring any financial interest in the company and must disclose any change in their proprietary or financial interests, if it occurs during the course of the study and for 1 year following study completion. The requirement for proprietary and financial disclosure also includes any ownership by the spouse or any dependent subject of the clinical investigator.

If FDA determines that the financial interests of any clinical investigator raise serious questions about the integrity of the data, FDA will take any action it deems necessary to ensure the reliability of the data, including:

- Initiating agency audits of the data derived from the clinical investigator in question
- Requesting that the sponsor submit further data analyses (eg, to evaluate the effect of the clinical investigator's data on overall study outcome)
- Requesting that the applicant conduct additional independent studies to confirm the results of the questioned study
- Refusing to treat the covered clinical study as providing data that can be the basis for an agency action

If the sponsor does not include certification or disclosure, or both (as required), or does not certify that it was not possible to obtain the information, the FDA may refuse to file the New Drug Application (NDA).

13 STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

It is anticipated that up to 130 subjects (approximately 50% in each treatment group) will be enrolled into the study.

A complete outline of the all planned analyses for the study, including the handling of missing data, is provided in the Statistical Analysis Plan for this protocol.

13.1 Estimand

The primary estimand for this study is the occurrence of intubation for the purpose of mechanical ventilation or surfactant administration in preterm neonates 28 to 32 weeks PMA in the modified intent-to-treat (mITT) population (all randomized subjects that received study medication). Intercurrent events include 1) treatment administration interruptions and 2) intubations for reasons other than MV or surfactant administration. Intercurrent events will evaluated using the hypothetical (primary analysis), treatment policy, and principal stratum strategies.

In regard to the hypothetical strategy (primary analysis), if a subject is intubated for a reason other than MV and/or surfactant administration (eg, surgical procedure, elective surgery), it is not possible to know if the subject would have ultimately required MV and/or surfactant administration. However, in order to maximize non-missing data, if the subject is extubated within 24 hours and did not receive surfactant while intubated, they will continue to be followed to determine if they have respiratory failure due to RDS (ie, intubated for MV and/or surfactant administration). Otherwise, they will not be counted in the denominator and their response to therapy will be considered missing for the primary analysis.

For the treatment policy strategy, the occurrence of either intercurrent event is irrelevant and the primary variable will be used regardless of whether an intercurrent event occurs.

Finally, for the principal stratum strategy, if a subject’s treatment was interrupted, there is an increased risk that the efficacy of the treatment will be impacted in a negative way. Thus, in the principal stratum strategy, these subjects will be excluded from the analysis. It should be noted that this strategy may lead to a biased estimation as interruptions, if they occur, can only occur with the active treatment. However, based upon testing of the current version of the ADS, it is expected that treatment interruptions will be exceedingly rare.

13.2 Statistical and Analytical Plans

The statistical analysis of both the primary and secondary objectives will be based on all enrolled preterm neonates who received study therapy. The first 2 subjects at each site, which were treated with open-label active therapy will be summarized separately. However, the safety data from these subjects may be pooled with the safety data from the subjects that received blinded therapy. The efficacy data will not be pooled.

For the efficacy analysis, all randomized subjects who received study therapy (modified intent-to-treat [mITT]) and subjects with no major protocol deviations (per-protocol) will be evaluated, based upon the treatment group to which they were randomized. If necessary, a population of subjects without treatment interruptions will also be defined and analyzed. For the safety analysis, all control subjects and subjects who received any amount of aerosolized lucinactant will be evaluated, based upon the treatment they actually received. All analyses will be performed for all subjects combined by treatment group and by gestational age strata.

All continuous variables (eg, weight, body temperature) will be summarized using number (n), mean, standard deviation (SD), median, 1st quartile, 3rd quartile, minimum, and maximum. All discrete variables (eg, sex, AEs, common complications of prematurity), will be summarized using frequency (n) and percent. Sites will be pooled for statistical analyses by geographic region.

The primary endpoint (the incidence of respiratory failure due to RDS or death within 28 days of life) is defined in Section 4.3.1. Respiratory failure due to RDS is defined as intubation (including intratracheal catheter placement) for MV and/or surfactant administration and will be compared between active treatment and control using the Cochran-Mantel-Haenszel (CMH) test, controlling for pooled sites.

Key secondary endpoints include the incidence of respiratory failure due to RDS within 72 hours, compared between active treatment and control using the CMH test; and time to respiratory failure due to RDS within 72 hours of life and 28 days of life, compared between treatments using the log-rank test, with pooled study site and treatment in the model. In addition, BPD, all-cause mortality, and common complications of prematurity (primarily air leak) will be compared using the Cochran-Mantel Haenszel test. Gas exchange parameters (ie, FiO_2, transcutaneous PCO_2) will be compared using ANOVA with pooled study site and treatment in the model.

The treatment difference (delta) between active and control treatments will be calculated for the primary and key secondary efficacy endpoints. The delta calculated will be used to plan additional studies and as supporting evidence of efficacy.

Demographic parameters will be summarized by treatment group and assessed qualitatively for homogeneity of treatment groups. Concomitant medications will be classified using the WhoDrug dictionary and summarized using frequency and percent.

AEs will be summarized by treatment group using frequency and percent. Physical examination and medical history will similarly be summarized. Vital signs (ie, body temperature, respiration rate, pulse) will be summarized as for continuous variables. AEs, physical examinations, and vital signs will not be compared statistically.

13.3 Interim Analyses

During the primary phase (screening to 36 weeks PMA), the chair of the DMC will receive regular reports on SAEs and AEs of interest (see Section 9.1) and DMC members will be updated on the program and trial status twice a year (outside of formal meetings) at spring and winter neonatology national meetings. In addition, there will be one planned meeting during study conduct, when enrollment is approximately 1/3 of the total enrollment of 70 (ie, approximately 28 subjects). An ad hoc meeting of the DMC will occur if the chair deems it necessary to address safety in the study.

The DMC may recommend that study enrollment be suspended if safety concerns are identified or suspected.

13.4 Sample Size and Randomization

A total of up to 130 study subjects (approximately 50% in each treatment group) will be enrolled.

Given that this is an estimation study, it is not powered to achieve statistical significance; however, based on the results from previous studies, it will be sufficient to show a qualitative improvement for the active group.

14 DATA COLLECTION, RETENTION AND MONITORING

All study data will be documented and reviewed within an eCRF, in accordance with local and regional regulatory requirements and ethical guidelines.

Before site initiation, all participating PIs must agree to permit study-related monitoring, audits, IRB/IEC reviews, as well as access and review of source data by Windtree or appointed designees.

All study members involved in study data capture and review must complete eCRF training relevant to their role before study start. Further details on data capture and eCRF completion is provided in the eCRF Completion Guidelines.

14.1 Protection of Subject Data and Confidentiality

To maintain subject confidentiality, only the site number and subject number will be used to identify all subjects on eCRFs and other documentation submitted to Windtree. All evaluation forms, reports, and other records will be identified by a coded number only.

All study records will be kept in a locked file cabinet and code sheets linking a subject's name to a subject identification number will be stored separately in another locked file cabinet. Clinical information will not be released without written permission of the subject's legally authorized representative, except as necessary for monitoring by the FDA. The investigators must also comply with all applicable privacy regulations (eg, HIPAA [US], EU Data Protection Directive 95/46/EC).

Additional subject confidentiality issues (if applicable) are covered in the Clinical Study Agreement.

14.2 Data Collection Instruments

The investigator will prepare and maintain adequate and accurate source documents designed to record all observations and other pertinent data for each subject enrolled in this study.

Study personnel at each site will enter data from source documents into the protocol-specific eCRF within 5 days of the information becoming available. Subjects will not be identified by name in the study database or on any study documents to be collected by Windtree (or designee) but will instead be identified by a site and subject number.

Corrections for an existing eCRF record will automatically be recorded by the eCRF system (audit trail capturing the time, date, and the identification of the user who entered or updated eCRF data). Recorded corrections by the eCRF will create an electronic audit trail of study documentation.

The PI is responsible for all study information obtained and documented on subjects. As such, the PI must review and verify all study data documented during the course of this study and ensure its completeness and accuracy.

14.3 Data Management Procedures

The data will be entered into a validated database. Members of Windtree's Data Management department are responsible for data processing, in accordance with procedural documentation. Database lock will occur once all quality assurance procedures have been completed; this will include but not be limited to the following: (1) all site-based study data have been entered into the eCRF, (2) all entered data have been reconciled and reviewed by Windtree or designee, and (3) all data related queries have been rendered and resolved.

All procedures for the handling and analysis of data will be conducted using good computing practices meeting FDA guidelines for the handling and analysis of data for clinical trials.

14.4 Data Quality Control and Reporting

After data have been entered into the study database, a system of computerized data validation checks will be implemented and applied to the database on a regular basis. Queries will be entered, tracked, and resolved through the electronic data capture (EDC) system directly. The study database will be updated in accordance with the resolved queries. All changes to the study database will be documented.

14.5 Archival of Data

The database is safeguarded against unauthorized access by established security procedures; appropriate backup copies of the database and related software files will be maintained. The databases will be backed up by a database administrator in conjunction with any updates or changes to the database.

At critical junctures of the study (eg, production of interim reports and final reports), data for analysis will be locked and cleaned per established procedures.

At the conclusion of the study, each investigative site will receive a CD of their final data.

14.6 Record Retention

All records that support data entered into the eCRF of each subject must be retained in the files of the PI or the hospital for a minimum of 2 years (3 years for ICF) following notification by Windtree

that all investigations have been discontinued or that the last approval of a marketing application has been obtained. Supporting documents will include but not be limited to the following:

1. Copies of eCRFs (given to the site on a CD)
2. All original source documents; these may include but not be limited to the following:
    a) ICFs
    b) laboratory reports
    c) progress notes
    d) medical histories
    e) physical and diagnostic findings
    f) diagnoses
    g) dates of therapy before and during this study
    h) drug and device dispensing/disposition records

If the PI retires, relocates, or for other reason withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. Windtree must be notified in writing of the name and address of the new custodian.

14.7 Monitoring

Windtree or their designee will perform on-site monitoring visits as frequently as it is deemed necessary to ensure quality study data capture, and accurate adherence to the study protocol as outlined in the study Monitoring Plan. In order to protect the blind, records that could unblind the monitor will be reviewed by an "unblinded monitor."

Before enrollment, a clinical site monitor will complete a site initiation visit (SIV) at each study site. During SIVs, clinical site monitors will provide study training to site staff, ensure study drug storage is in accordance with the study protocol, and validate all other study requirements in accordance with the study monitoring plan.

Clinical site monitors will schedule a study site visit as close as possible to the time of each site's first enrolled study subject; periodic follow-up monitoring visits will ensure on a regularly scheduled basis throughout the study, in accordance with enrollment at the study site. At these visits, the clinical site monitor will compare the data entered into the eCRF with the hospital or clinic records (source documents) and check for protocol compliance. Documentation reviews will include but not be limited to the evaluation and confirmation of the following:

1. A record of informed consent
2. Adherence to enrollment criteria
3. Completion of all required study assessments
4. Accurate and complete data capture of all AEs, concomitant medications, and safety and efficacy observations.
5. Study drug and ADP storage and dispensing records maintained in accordance with study and regulatory requirements.

Findings from these reviews will be discussed with the PI and study site staff.

The dates of the monitoring visits will be recorded by the clinical site monitor in a sign-in log to be kept at the site. The study coordinator and PI are expected to be available for questions, have all source documentation readily available, and have a suitable environment provided for review of study-related documents.

In accordance with ICH E6, Windtree will select (either directly or through a subcontract with a company specifically trained in the monitoring of clinical studies), qualified individuals to monitor study sites to ensure the quality of study progress and the close adherence of study sites to the study protocol and all related governing documents and SOPs.

The clinical site monitor(s), before the initiation of each study site, will ensure each investigator and study staff understands the following:

a) The investigational status of the study drug and device components and the requirements for its accountability

b) The need to uphold all directives within the clinical protocol as it relates to study conduct and subject safety at the study site

c) The obligation to obtain informed consent in accordance with the Declaration of Helsinki and ICH GCP guidelines before enrolling each subject in the study

d) The obligation to obtain IRB/IEC review and approval of the study before study initiation at his/her clinical site and ensure timely updates to the IRB/IEC as mandated by local and national regulatory requirements, and to ensure timely communications to Windtree of all IRB/IEC communications (to include reviews and subsequent actions) concerning the study.

The clinical site monitor(s) will perform periodic visits to each clinical site during the course of the study to ensure the study protocol is being followed and that:

a) Drug and device inventories are being properly maintained and documentation of vial usage is accurate and complete (unblinded monitor only).
b) The PI is reporting all serious or fatal AEs (Section 9.1.4) as soon as possible, and in no case later than 24 hours after the event, to the medical monitor or designee at Windtree.
c) Site reports temperature excursions for drug product; complaints for drug and device are reported (unblinded monitor only).

The clinical site monitor(s) will perform an end-of-study visit to each clinical site to ensure that:

a) All drug and device reconciliation forms, as provided in the study manual, are accurate and complete.
b) All used and unused vials of study drug have been reconciled.
c) All eCRFs are complete and all monitoring of eCRFs has been completed.

15 ADMINISTRATIVE AND REGULATORY CONSIDERATIONS

This study will be conducted according to the US and ICH regulations and guidelines (21 CFR 50, 21 CFR 56, 21 CFR 312, and ICH E6*)* as well as all applicable local, state, and federal regulations and guidelines regarding the conduct of clinical studies. In addition, this study will be conducted in accordance with the ethical principles included in the WMA Declaration of Helsinki.

15.1 Protocol Amendments

Any amendments to the protocol will be written by Windtree. Protocol amendments will not be implemented without prior written IRB/IEC approval except as necessary to eliminate immediate safety hazards to study subjects. A protocol amendment intended to eliminate an apparent immediate hazard to study subjects may be implemented immediately, provided the IRB/IEC is notified within 5 working days.

15.2 End-of-Study Procedures

The PI will complete all required end-of-study procedures as outlined in the study manual and submit the final eCRFs (in satisfactory compliance with the protocol) within 1 week after the last subject at this site has completed the study. Continuation of this study beyond this time must be agreed upon by both the PI and Windtree and may be implemented without amendment to the protocol.

15.3 Study Report

Windtree will take full responsibility for signing the final report following consultation with the steering committee.

15.4 Publications

The preparation and submittal for publication of a manuscript containing the study results shall be in accordance with a process determined by a mutual written agreement among Windtree and participating institutions. The publication or presentation of any study results shall comply with all applicable privacy laws, including but not limited to HIPAA.

15.5 Investigator Responsibilities

By signing the Investigator Agreement Form (Appendix 2 - Investigator Agreement Form), the PI agrees to:

1. Conduct the study in accordance with the protocol and only make changes after notifying Windtree or designee, except when to protect the safety, rights or welfare of subjects.
2. Personally conduct or supervise the study (or investigation).
3. Use the drug and/or device only for the purpose of investigational testing specified in the protocol, and not permit the device to be used by any other person except under my direction.
4. Ensure that the requirements relating to obtaining informed consent and IRB/IEC review and approval meet federal guidelines, as stated in 21 CFR 50 and 21 CFR 56.
5. Report any AEs/SAEs that occur in the course of the study to Windtree or designee, in accordance with 21 CFR 312.64.
6. Maintain adequate and accurate records in accordance with 21 CFR 312.62 and to make records available for inspection by Windtree, designee, or Regulatory Agency.
7. Ensure the study site is fully aligned with their local IRB/IEC.
8. Ensure the local IRB/IEC complies with the requirements of 21 CFR 56 and/or ICH E6 guidelines and as such will be responsible for initial and continuing review and approval of the clinical study protocol and related documents.
9. Promptly report to the IRB/IEC and Windtree or designee all changes in the research activity and all unanticipated problems involving risks to subjects or others (to include amendments and Investigational New Drug [IND] safety reports).
10. Seek IRB/IEC approval before any changes are made in the research study, except when necessary to eliminate hazards to the study subjects.
11. Comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements listed in 21 CFR 312 and in applicable local regulations.
12. Ensure that all associates, colleagues, and employees assisting in the conduct of the study are informed about their obligations in meeting the above commitments.

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17 APPENDICES

Appendix 1 - Protocol Definitions

Definitions	
Air leak, pulmonary	Chest radiographic evidence of air leak (pneumothorax, PIE, pneumomediastinum, pneumopericardium, subcutaneous emphysema). An air leak is considered an AE of special interest if it occurs at any time during the study.
Apnea	A lack of inspiratory air movement sustained for ≥ 20 seconds and coincident with at least one of the following: (a) SpO_2 < 80% (not necessarily ≥ 20 seconds), (b) HR < 100 bpm (not necessarily ≥ 20 seconds), or (c) requirement for positive pressure ventilation administered manually or mechanically through any patient interface.
Bradycardia	A heart rate < 100 bpm sustained for ≥ 20 seconds
Bronchopulmonary dysplasia (BPD)	The need for oxygen supplementation (FiO_2 > 0.21), regardless of source, at 36 weeks PMA.
Desaturation	SpO_2 < 80%, sustained for ≥ 20 seconds
Final Visit	The final study visit is to occur at 36 weeks PMA (or 28 days of life, whichever occurs last), at the time of hospital discharge, or at the time of hospital transfer (whichever occurs first). If the neonate dies, the final visit will be considered the last study data reported before death.
Gestational age	Gestational age of the subject based on the mother's last menstrual period (post-menstrual age [PMA]) based on best obstetrical estimate or ultrasound.
Non-invasive ventilation (NIV)	Any respiratory support device which generates a constant or variable (eg, bi-level) positive pressure regardless of whether synchronized to the subject's inspirations and uses a patient interface on the subject's face.
Study treatment	Receipt of active or sham treatment, either initially or as a repeat. Masking procedures for the initial treatment will be followed for repeat treatments.
Oxygen-only support	Delivery of oxygen without the generation of pressure above ambient pressure (eg, standard-flow nasal cannula). Although all forms of respiratory support may provide FiO_2 > 0.21, for this study oxygen-only support refers to modes that deliver oxygen without pressure.

Appendix 2 - Investigator Agreement Form

Study Title:	A Multinational, Multicenter, Masked, Randomized, Parallel Group, Controlled Study to Assess the Safety and Efficacy of Lucinactant for Inhalation versus nCPAP alone in Preterm Neonates 26 to 32 Weeks Gestational Age with Respiratory Distress Syndrome
Study Number:	03-CL-1702

I have read the foregoing protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure they are fully informed regarding the study drugs and/or devices and the conduct of the study.

I will use only the informed consent form approved by the Institutional Review Board/Independent Ethics Committee and Windtree Therapeutics, Inc. (Windtree) and will fulfill all responsibilities for submitting pertinent information to the IRB/IEC responsible for the study.

I further agree that authorized representatives of Windtree, the US Food and Drug Administration, or other regulatory agencies will have access to any source document from which eCRF information may have been generated.

I agree that I and all subinvestigators listed on the delegation of authority form and/or Form FDA 1572 shall inform Windtree of any equity interest in the company prior to participating in this study. I further agree that I and all subinvestigators listed will consult with Windtree before acquiring any financial interest in the company during the study and for one year after the study's completion.

Signed:_____ Date:_____

Printed Name: _____

Title: _____

Affiliation: _____

Address: _____

_____

Phone Number: _____