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

Protocol No.:	03-CL-1202
Study Phase:	2b
Investigational Product:	AEROSURF® (lucinactant for inhalation)
IND Number:	119438
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A Multinational, Multicenter, Masked, Randomized, Controlled Study to Assess the Safety and Efficacy of Lucinactant for Inhalation in Preterm Neonates 26 to 32 Weeks Gestational Age with Respiratory Distress Syndrome

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LUCINACTANT FOR INHALATION PROTOCOL SUMMARY

Protocol Number	03-CL-1202
Title:	A Multinational, Multicenter, Masked, Randomized, Controlled Study to Assess the Safety and Efficacy of Lucinactant for Inhalation in Preterm Neonates 26 to 32 Weeks Gestational Age with Respiratory Distress Syndrome
Phase:	2b
US IND Number:	119438
Sponsor:	Discovery Laboratories, Inc. (Discovery), Warrington, PA, USA
Committees:	Steering Committee, Data Monitoring Committee (DMC)
Study Drug and Device:	Lucinactant for inhalation (an investigational, drug-device combination product) at 30 mg total phospholipids (TPL)/mL 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 dipalmitoylphosphatidylcholine (DPPC), palmitoyloleoyl-phosphatidylglycerol, sodium salt (POPG, Na), and the fatty acid palmitic acid (PA).
Rationale:	Respiratory distress syndrome of the newborn (RDS) 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 replacement therapy (SRT) reduces mortality and morbidity in preterm infants with RDS and is recommended by multiple international guidelines. Currently, SRT requires endotracheal intubation to instill surfactant directly into the neonate's lung, often with concomitant positive pressure mechanical ventilation (MV). However, both intubation and MV may have deleterious effects to the infant, potentially leading to short- or

long-term morbidities.

In order to avoid endotracheal intubation 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. SRT, however, cannot be delivered with nCPAP. Although sometimes successful, nCPAP will fail in approximately one-third to one-half of preterm neonates, who generally then require endotracheal intubation, MV, and in many cases delayed administration of SRT. Earlier SRT is more effective than later 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 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.

To address this unmet need, Discovery Laboratories, Inc. (Discovery) has 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. 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). The device component, the Aerosurf® Delivery System (ADS), uses novel technology to aerosolize lucinactant for inhalation.

Lucinactant for inhalation was studied in preterm neonates 29 to 34 weeks PMA in an open-label safety study (Protocol 03-CL-1201) at escalating dosages of 25, 50, 75, 100 and 150 mg total phospholipids (TPL)/kg. In 80 neonates (8 in each of the 5 active groups and 40 in the control group), lucinactant for inhalation was generally well tolerated and there were generally no safety signals of concern with escalating doses. Complications of prematurity, including pulmonary air leak, were comparable between treatment and control groups. Exploratory assessment of clinical efficacy parameters suggests that lucinactant for inhalation may be providing beneficial effects.

A similar dose escalation study in preterm infants 26 to 28 weeks PMA has been initiated (Protocol 03-CL-1401) and is ongoing, using escalating dosages of, 50, 75, 100 and 150 mg total phospholipids (TPL)/kg. In 45 neonates to date (8 each in the 50 and 75 mg TPL/kg groups, 6 in the 100 mg TPL/kg group and 23 in the control group), lucinactant for inhalation has been generally well tolerated and there have been generally no safety signals of concern with escalating doses. Complications of prematurity, including pulmonary air leak, have so far been comparable between treatment and control groups. Exploratory assessment of clinical efficacy parameters to date suggests that it is likely that lucinactant for inhalation at a dosage greater than 100 mg TPL/kg (repeated more than 1 time) may be required in this population to provide beneficial effects.

Going forward, Discovery has decided to develop and evaluate dosages of 40 and 80 mg TPL/kg. Results from preclinical and clinical trials, including Study 03-CL-1201 and Study 03-CL-1401, support the safety and potential efficacy of initial and repeat administration with these dosages.

Objectives: To evaluate the safety and efficacy of lucinactant for inhalation 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 and/or death due to RDS in the first 72 hours of life, the incidence of bronchopulmonary dysplasia (BPD) at 36 weeks PMA, and change in physiologic parameters (fraction of inspired oxygen [FiO_2] and partial pressure of carbon dioxide [PCO_2]) over the first 72 hours of life.

Primary Endpoint: The primary endpoint for this study is the incidence of respiratory failure or death due to RDS within the first 72 hours of life. A subject will be categorized as having respiratory failure due to RDS if either of the following occur:

1. Intubation for MV and/or surfactant administration (with or without MV) within 72 hours of life
2. The subject meets at least 1 of the following criteria, regardless of whether endotracheal intubation is performed:
   a. A sustained ($\geq$ 60 minutes) need for $FiO_2 > 0.45$ to maintain an SpO_2 > 90% to 95%

b. A sustained (on ≥ 2 consecutive observations > 60 minutes apart) transcutaneous PCO_2 > 65 mm Hg
c. nCPAP > 8 cm H_2O

Death due to RDS is any death whose primary cause is respiratory failure due to RDS.

Secondary Endpoints:

The secondary endpoints of this study include the evaluation of the following from the time of initiation of study treatment until study completion:

1. Time to respiratory failure or death due to RDS
2. Incidence rate of BPD at 36 weeks PMA
3. All-cause mortality
4. Incidence rate of survival without BPD at 36 weeks PMA
5. Incidence rate of pulmonary air leak

Tertiary Endpoints

The tertiary endpoints of this study include the evaluation of the following from the time of initiation of study treatment until study completion:

1. Incidence rates of common complications of prematurity other than air leak
2. Change from baseline in FiO_2 and/or transcutaneous PCO_2 over the first 72 hours of life

Study Design:

This study is a sequential, 2-part, multinational, multicenter, masked (Part A)/open-label (Part B), randomized, controlled study to evaluate the safety and efficacy of lucinactant for inhalation in conjunction with nCPAP compared with nCPAP alone, in preterm neonates 28 to 32 completed weeks PMA (Part A) and in preterm neonates 26 to 28 completed weeks PMA (Part B) who are being cared for in a neonatal intensive care unit (NICU), who had successful implementation of non-invasive respiratory support or ventilation within 90 minutes of birth (60 minutes for Part B), and who are candidates for SRT. The preferred initial mode of support is study nCPAP; however, other 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 Parts A and B of the study, a primary phase through 36 weeks PMA and a longer-term follow-up phase through 1-

year corrected age. Data will be analyzed and reported at the completion of each respective study phase for Parts A and B of the study.

Before study enrollment, legal guardians will provide a signed written informed consent form (ICF) for each potential subject. 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 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.

For Part A of the study, inclusion criteria to be met within the first 20 hours after birth include respiratory insufficiency with a requirement for nCPAP of 5 to 7 cm H_2O with a FiO_2 ≥0.25 (>0.21 for neonates 28 weeks PMA) to 0.4 to maintain oxygen saturation measured by pulse oximetry (SpO_2) of 90% to 95% for at least 30 minutes. For Part B of the study, inclusion criteria to be met within the first 12 hours after birth include respiratory insufficiency with a requirement for nCPAP of 5 to 7 cm H_2O with a FiO_2 >0.21 to 0.4 to maintain SpO_2 of 90% to 95% for at least 20 minutes. As soon as study qualification has been confirmed and the informed consent is signed, subjects will be randomized to an active treatment group (2 active groups in Part A; 1 active group in Part B) or to the control group (nCPAP only, with simulated ["sham"] study drug treatment in Part A). Study treatment (lucinactant for inhalation or sham/control) must be initiated as soon as possible and no more than 2 hours after randomization.

Subjects in Part A may be eligible to receive up to 2 repeat doses of the treatment to which they are originally assigned, and subjects in Part B may receive up to 4 repeat doses. Repeat doses will be given for subjects in Part A as soon as 2 hours, and for subjects in Part B as soon as 30 minutes, from completion of the previous dose up to 36 hours after completion of randomization if subjects meet repeat dosing criteria (as described in the "Treatment Groups" section) unless it is unsafe to do so in the judgment of the investigator. Subjects randomized to the control group will be continued on nCPAP alone; subjects in Part A will receive repeated sham treatment to maintain study masking, while subjects in Part B will receive open label treatment.

In both parts of the study, all subjects in the active treatment groups will

receive the same drug concentration of lucinactant for inhalation (30 mg TPL/mL) at the same rate of delivery (aerosolized concentration of 4.2 mg TPL/L in aerosol carrier gas flow of 3 L/min). The dosage will vary by the predetermined administration time for each dosage (25 minutes for the 40 mg TPL/kg arm in Part A, 50 minutes for the 80 mg TPL/kg arm in Parts A and B). Lucinactant for inhalation will be delivered by the investigational ADS device in conjunction with a commercially available nCPAP generator and patient interface. Dose assignments in Part A will be masked from the principal investigator (PI), clinical and study staff (eg, site coordinator, bedside nurse), as applicable; sponsor as applicable; and subject's parents/legal guardians. Dose assignments in Part B will be open label.

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.

In both parts of the study, neonates will be followed for the primary phase efficacy and safety evaluations through 36 weeks PMA, NICU discharge, hospital transfer, or death (whichever occurs first). For the longer-term follow-up phase, neonates will be evaluated by phone or visit at 6-months corrected age and followed up to 1-year corrected age, at which time a physical examination will be performed, including an abbreviated neurologic assessment.

Study Population: The study population will be comprised of preterm neonates 26 to 32 completed weeks PMA who are receiving care in a NICU and are receiving nCPAP as the primary support modality for RDS. Enrollment will be conducted by strata: in Part A, approximately 5-10% of the subjects will be 28 completed weeks PMA and the remainder will be 29 to 32 completed weeks PMA, while in Part B randomization will be stratified by gestational age (26, 27, and 28 completed weeks PMA).

	The study population in Part A will be randomized in a 1:1:1 ratio into 1 of 3 treatment groups, and in Part B 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 240 study subjects (up to 80 per treatment group) will be enrolled in Part A, and up to 80 subjects (up to 40 per treatment group) will be enrolled in Part B. For Part A, the sample sizes were calculated separately for incidence of respiratory failure due to RDS, time to respiratory failure or death due to RDS, and a reduction in FiO_2. The sample size will have 90% power to detect the difference between treatment groups using a log-rank test for equality of time to event curves, assuming a constant hazard ratio of 0.500, within the first 72 hours of life. In addition, the sample size is sufficient to detect, separately, a reduction of 50% in the incidence of respiratory failure or death due to RDS within the first 72 hours of life, or a reduction in FiO_2 of 4 percentage points (eg, 30% to 26%) within the first 24 hours following treatment. In addition, the sample size should be sufficient to provide a stable estimate of the size of the treatment effect (treatment delta). The efficacy estimate will be used to calculate the sample size for future studies. For Part B, formal sample size calculations have not been conducted. A total of 40 subjects per group should be sufficient to provide a stable estimate of the size of the treatment effect.
Number of Sites:	Approximately 60 study sites in North America, Europe, and South America.
Study Duration:	Overall, study enrollment will be completed in approximately 18 to 20 months, with the last subject completing his or her last visit approximately 20 to 22 months from the time the first subject enrolled. Subject participation will be from ≤20 hours following birth until 36 weeks PMA, NICU discharge, death, or hospital transfer, whichever occurs first for the primary evaluation phase of the study. Follow-up through 1-year 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 continue to receive nCPAP alone; in order to maintain masking in Part A, "sham" study drug treatment will be used: the ADS will be brought to the bedside but will not be used, and no active 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. Because of losses that occur as the lucinactant aerosol travels from the ADS to the patient interface, approximately 35% of the reconstituted lucinactant aerosolized by the ADS is emitted and available to be inhaled.

Treatment Groups:

Part A:

40 mg/kg	40 mg TPL/kg administered over 25 minutes in conjunction with nCPAP (n=80) Up to 2 repeat doses of 40 mg TPL/kg administered over 25 minutes will be given if repeat dosing criteria are met.
80 mg/kg	80 mg TPL/kg administered over 50 minutes in conjunction with nCPAP (n=80) Up to 2 repeat doses of 80 mg TPL/kg administered over 50 minutes will be given if repeat dosing criteria are met.
Control	Continuous nCPAP (n = 80) with sham drug treatment Up to 2 repeat sham treatments will be given if repeat dosing criteria are met.

Part B

80 mg/kg 80 mg TPL/kg administered over 50 minutes in conjunction with nCPAP (n = up to 40)

Up to 4 repeat doses of 80 mg TPL/kg administered over 50 minutes will be given if repeat dosing criteria are met.

Control Continuous nCPAP (n = up to 40)

Repeat dosing will be given ≥2 hours (≥30 minutes for Part B) from completion of the previous dose up to 36 hours after completion of randomization if subjects have a sustained (≥30 minutes) need for FiO_2 above the qualifying FiO_2 for study enrollment (≥0.25 for neonates 29-32 weeks PMA, >0.21 for neonates 26-28 weeks PMA) to maintain SpO_2 of 90% to 95%, unless it is unsafe to do so in the judgment of the investigator. In Part A, masking procedures for the initial dose will be followed for repeat doses, including controls.

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 (consent may be obtained prenatally, where allowed)
2. Gestational age:
    a. Part A: 28 0/7 to 32 6/7 completed weeks' gestation PMA
    b. Part B: 26 0/7 to 28 6/7 completed weeks' gestation PMA
3. Successful implementation of non-invasive support or ventilation (preferably bubble CPAP) within:
    a. Part A: 90 minutes after birth
    b. Part B: 60 minutes after birth
4. Spontaneous breathing
5. Chest radiograph consistent with RDS (may be deferred if in the best medical interest of the subject)
6. Respiratory support:
    a. Part A: Within the first 20 hours after birth, requires an nCPAP of 5 to 7 cm H_2O with an FiO_2 ≥0.25 (>0.21 for neonates 28 weeks PMA) to 0.4 that is clinically indicated for at least 30 minutes to maintain SpO_2 of 90% to 95%.

b. Part B: Within the first 12 hours after birth, requires an nCPAP of 5 to 7 cm H_2O with an FiO_2 of >0.21 to 0.4 that is clinically indicated for at least 20 minutes to maintain SpO_2 of 90% to 95%.

Transient (<10 minutes) FiO_2 excursions outside this range do not reset the time requirement.

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 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 (PROM) >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 already received)
11. Presence of air leak (pneumothorax, pneumomediastinum, pneumopericardium, subcutaneous emphysema, or definite evidence of pulmonary interstitial emphysema [PIE]) on the baseline chest radiograph

Concomitant Medications:

All concomitant medications administered to the subject from birth until 36 weeks PMA, NICU 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. 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. Caffeine or other methylxanthines are recommended.

Safety and Tolerability Endpoints:

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

1. Survival (date and time of death, if applicable)
2. AEs, including adverse device effects (ADEs) and AEs of special interest including peri-dosing events, complications related to placement of bi-nasal prongs, and air leak
3. Concomitant medications
4. Use of respiratory support and supplemental O_2, including the following:
    a. Need for endotracheal intubation and MV
    b. Mode of respiratory support (including supplemental oxygen) and important parameters for that mode
5. Complications of prematurity
6. Physical examinations
7. Tolerability of lucinactant for inhalation
8. Incidence of air leak
9. Assessments of the following:
    a. Vital signs
    b. O_2 saturation, as determined by pulse oximetry (SpO_2)
    c. Serum electrolyte measurements
    d. Defecation
    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 error codes occur 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 failure or malfunction occurs, including certain error codes
2. An AE or ADE which places subject safety occurs, eg pulmonary hemorrhage
3. 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
4. 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) An $FiO_2 \geq 0.70$ or sustained increase from baseline by ≥ 0.30 to maintain SpO_2 90% to 95%
   b) A transcutaneous $PCO_2 > 70$ mm Hg or a progressive increase from baseline to ≥ 20 mm Hg above baseline
   c) Recurring episodes of bradycardia
   d) A sustained apneic event

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.

Statistical Analysis

The statistical analysis of both the primary and secondary objectives will be based on all enrolled preterm neonates. For the efficacy analysis, populations of all randomized subjects who received any treatment (intent-to-treat [ITT]) and subjects with no major protocol deviations (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. All analyses will be performed for Parts A and B of the study for all subjects combined and by gestational age strata.

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.

Interim Analyses: The data monitoring committee (DMC) will conduct 2 preplanned interim analyses during Part A of the study: 1) after approximately 25% of subjects have been enrolled and 2) after 66% of subjects have been enrolled. The DMC will be provided full safety tables and listings for review after 20 subjects have been enrolled in Part B, but will not conduct a formal interim analysis. Study enrollment may be suspended if safety concerns are identified during the review.

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

Abbreviation	Description
ACU	AEROSURF® Control Unit
ADE	Adverse device effect
ADS	AEROSURF® Delivery System
ADP	AEROSURF® Delivery Pack
AE	Adverse event
BPD	Bronchopulmonary dysplasia
CAG	Capillary-based aerosol generator
CFR	Code of Federal Regulations
CPAP/nCPAP	Continuous positive airway pressure/nasal CPAP
CRF/eCRF	Case report form/electronic CRF
DMC	Data Monitoring Committee
DPPC	dipalmitoylphosphatidylcholine
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 Harmonization
IEC/IRB/REB	Independent Ethics Committee/Institutional Review Board/Research Ethics Board
IMV	Intermittent mechanical ventilation
IND	Investigational new drug
IPP	Intermittent positive pressure
ITT	Intent-to-Treat
IVH	Intraventricular hemorrhage
IWRS	Interactive web response system

Abbreviation	Description
KL_4	21-amino acid hydrophobic synthetic peptide, also known as sinapultide
MMAD	Mass median aerodynamic diameter
NDA	New drug application
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
PIF	Peak inspiratory flow
PMA	Post-menstrual age
POPG, Na	Palmitoyloleoyl-phosphatidylglycerol, sodium salt
PROM	Premature rupture of membranes
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
SRC	Safety review committee
SRT	Surfactant replacement therapy
TORCH	Toxoplasmosis, rubella, cytomegalovirus, herpes simplex
TPL	Total phospholipids
UADE	Unanticipated adverse device effect
US	United States
Vm	Minute ventilation
WMA	World Medical Assembly

1 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 intended 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 doses of 40 or 80 mg total phospholipids (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 in preterm infants 26 to 28 weeks PMA has been initiated (Protocol 03-CL-1401). To date, there have been no safety signals of concern. Findings from these 3 studies (03-CL-1201, 03-CL-1401, and 03-CL-1202) 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)/research ethics board (REB) requirements, International Conference on Harmonisation Good Clinical Practices (ICH GCP) Guidelines, and local institutional practices.

Definitions of study terms are provided in Appendix 1.

1.1 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 (3-6). 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, 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), and may also contribute to development of chronic lung disease (CLD) / bronchopulmonary dysplasia (BPD) (10).

1.1.1 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 nasal continuous positive airway pressure (nCPAP) as an effective means of providing ventilatory support is now accepted practice (3-6, 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, VapoTherm, SiPAP) 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 (13-16), 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 day 28 after birth) 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 was greater in the nCPAP groups compared to the intubation groups (12-14). 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.

1.1.2 Unmet Medical Need for Aerosolized Surfactant Replacement Therapy

Several studies have demonstrated that earlier intratracheal SRT is more beneficial than later SRT (2). For this reason, guidelines recommend that when SRT is used it be given as early as possible (3-6). 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.

1.2 Development of Aerosolized Surfactant with Lucinactant for Inhalation

To address this unmet need, Discovery Laboratories, Inc. (Discovery) has 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 referred to as 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). The ADS uses novel capillary-based aerosol generator (CAG) technology to aerosolize lucinactant for inhalation, providing a high-density surfactant aerosol output (1.2 mL/min), with an appropriate particle size (2 to 3 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 effect 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.

1.3 Clinical Experience with Aerosolized Lucinactant

Two Discovery-sponsored clinical studies have been conducted using aerosolized lucinactant administered with standard, commercially available nebulizers (Studies KL4-CPAP-01 (27) and KL4-ASTH-01). Aerosolized lucinactant administered with the ADS has been investigated in one completed Discovery-sponsored clinical trial (Study 03-CL-1201) and one ongoing Discovery-sponsored clinical trial (Study 03-CL-1401). These studies are described below, and in further detail in the Investigator's Brochure.

1.3.1 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 dose 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, ≤ 24.5 mg TPL was administered at approximately 1 mg/minute. The treatment was well-tolerated with no serious adverse events (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.

1.3.2 Clinical Studies using the AEROSURF Delivery System

Lucinactant aerosolized using the ADS has been studied in a completed Phase 2a study in infants 29 to 34 weeks PMA (Study 03-CL-1201). Results of this study are summarized in Section 1.3.2.1, and results apropos to the selection of dosages in Part A of this study are summarized in Section 2.2.3.5. In addition, another study (Study 03-CL-1401) has been initiated to evaluate the safety and tolerability of lucinactant for inhalation in younger preterm infants 26-28 completed weeks PMA. Preliminary results of this study are summarized in Section 1.3.2.2, and results apropos to the selection of dosages in Part B of this study are summarized in Section 2.2.3.5. The current protocol (03-CL-1202) is designed to evaluate the size of the treatment effect for planning future studies.

1.3.2.1 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 aerosolized lucinactant delivered using the ADS in preterm infants 29 to 34 completed weeks PMA. This study was conducted at 12 study sites in the US and evaluated the safety of 5 dose-exposures of aerosolized lucinactant in conjunction with nCPAP: 25 mg TPL/kg, 50 mg TPL/kg, 75 mg TPL/kg, 100 mg TPL/kg and 150 mg TPL/kg. Repeat doses were possible for the larger 2 dosages. Neonates treated with nCPAP alone served as the control group.

A total of 80 neonates were enrolled, with 8 in each of the 5 dosing groups and 40 in the control group. Active and control subjects were similar in terms of gestational age, birth weight, gender, race and ethnic origin. One subject did not meet inclusion criteria but was enrolled in error; since this subject was randomized to the 100 mg TPL/kg group and briefly received study treatment, this subject was included in the safety analysis but not in the exploratory efficacy analyses. 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 (including the subject enrolled in error); and 2 (5%) due the principal investigator’s medical judgment. “Device failure or malfunction” was selected when the ADS terminated aerosol treatment early; however, these early stoppages were due to an error code being detected, such as an aerosol temperature outside of the preset

acceptable range. Thus, the device functioned as designed, but the full treatment was not delivered.

The incidence of adverse events (AEs) was comparable between treatment and control groups, occurring in 39 (98%) active subjects and 37 (93%) controls. The incidence of AEs did not increase with dosage. The 3 most common AEs were neonatal jaundice, constipation and neonatal apnea. Complications of prematurity were comparable between treatment and control groups; the 3 most common were apnea (occurring in 23 [58%] active and 23 [58%] control subjects), air leak (9 [23%] active and 7 [18%] controls, discussed further below), and patent ductus arteriosus (5 [13%] active and 3 [8%] control subjects). Peri-dosing events were uncommon, occurring in 7 (18%) active subjects with no increase in incidence as dosage increased. 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. SAEs occurred in 13 (33%) of active subjects, with no increase in incidence as dosage increased, and 7 (18%) of control subjects. Pneumothorax (a specific form of air leak, discussed further below) was the most commonly reported SAE, reported in 9 (23%) active subjects and 4 (10%) controls. 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 (Curosurf) 2 days after randomization into the study; neither death was considered to be related to study treatment or procedures.

When all forms of pulmonary air leak, including pneumothorax, pneumomediastinum and PIE (see Section 9), are considered together, the incidence in active and control groups was similar (Table 1-1). 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.

Table 1-1: Air Leaks Reported as Adverse Events in Study 03-CL-1201

	25 mg TPL/kg (N=8)	50 mg TPL/kg (N=8)	75 mg TPL/kg (N=8)	100 mg TPL/kg (N=8)	150 mg TPL/kg (N=8)	Total Active (N=40)	nCPAP Only (N=40)
Total Air Leaks[1]	2 (25%)	2 (25%)	1 (13%)	2 (25%)	2 (25%)	9 (23%)	7 (18%)
Pneumothorax	2 (25%)	2 (25%)	1 (13%)	2 (25%)	2 (25%)	9 (23%)	5 (13%)
Pneumomediastinum	0	1 (13%)	0	0	0	1 (3%)	0
PIE	0	0	0	0	2 (25%)	2 (5%)	2 (5%)

[1]Subjects may have had more than one type of air leak
PIE = pulmonary interstitial emphysema

Lucinactant for inhalation had no clinically important effect on serum electrolytes, gastric liquid volume, or defecation. Mean concentration of serum electrolytes (sodium, potassium, chloride, total carbon dioxide) was within normal range in active patients at 24 hours of life. AEs related to electrolyte disturbances were infrequent (≤13%) and similar between active and control subjects. Gastric liquid volume (residual) checked after dosing was physiologically normal for all active subjects, ranging from 0.00 to 8.00 mL; mean volume tended to increase with dosage (0.25±0.5 mL in the 25 mg TPL/kg group, 2.00±1.9 mL in the 150 mg TPL/kg group). Although constipation was reported an AE somewhat more frequently in active subjects (50%) vs controls (35%), active subjects had a physiologically normal number of stools (1.9) in the first 24 hours of life which was similar to the number in control subjects (1.7).

Study 03-CL-1201 was neither designed nor powered to investigate efficacy. However, clinical parameters associated with efficacy (and safety) were measured. Preliminary results are described here for completeness and to inform dosage selection for the present study (see Section 2.2.3). Overall, active subjects had a more rapid decrease in FiO_2 than control subjects (Figure 1-1): 1 hour after starting dosing, 11 (28%) active subjects were breathing room air (FiO_2 0.21) vs 3 (8%) control subjects. Decreases in FiO_2 were modest as expected (Figure 1-1), since most subjects were on relatively small amounts of supplemental oxygen (median FiO_2 0.28 in active subjects, 0.30 in controls). Decreases in PCO_2 were similarly modest and not different between actives and controls.

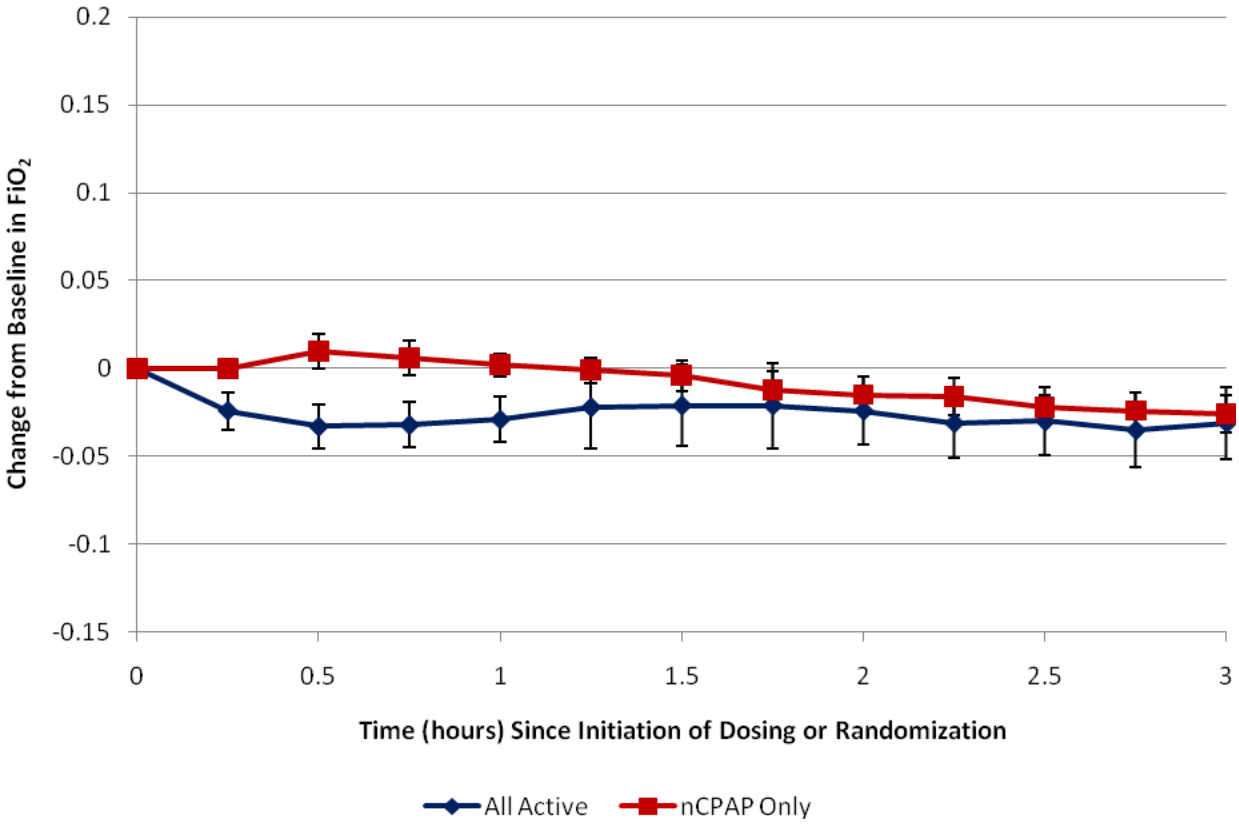

Figure 1-1 Change from baseline in FiO_2 of all subjects in Study 03-CL-1201

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 aerosolized surfactant seeks to avoid. When limited to the initial 72 hour period, intubation occurred in 21 (53%) of control subjects (Figure 1-2); 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%). Additionally, time to intubation was longer in active subjects (mean±SE of 55±36 hrs) than controls (19±4 hrs), particularly for subjects in the higher 3 dosage groups (Figure 1-3).

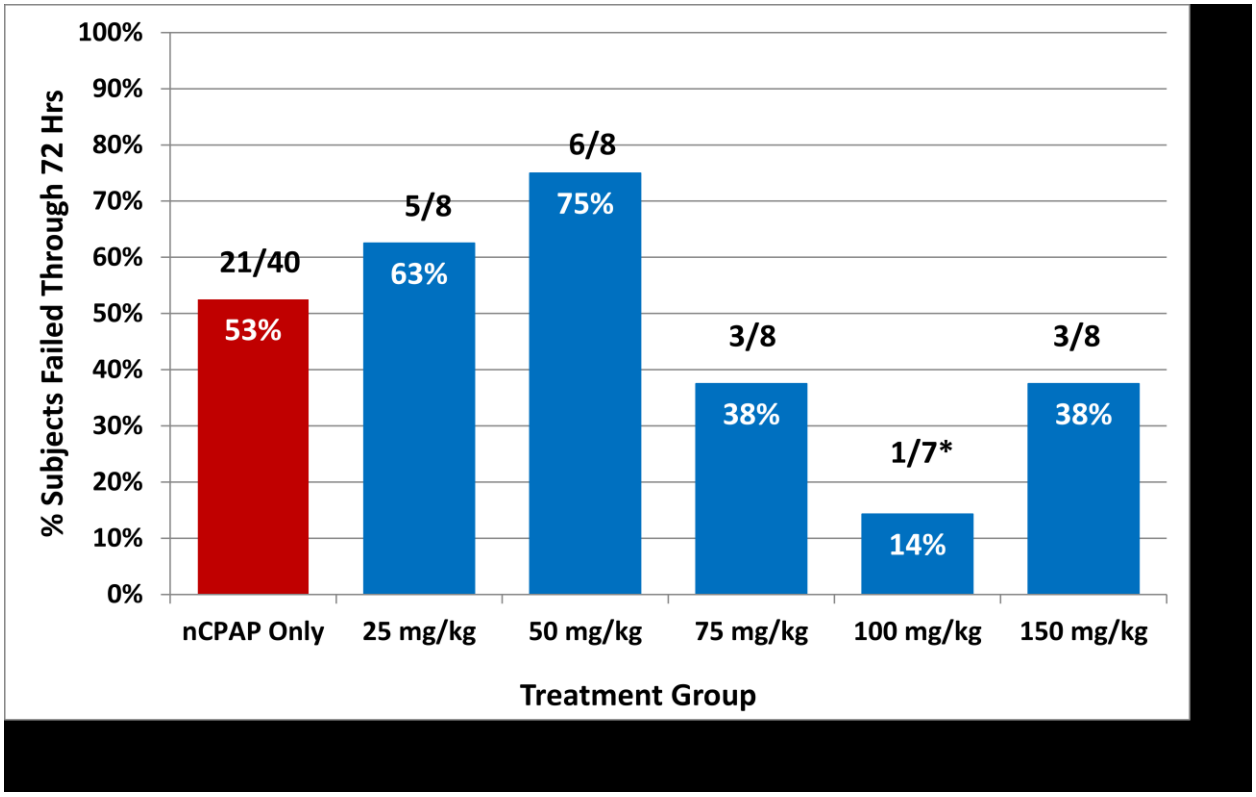

Figure 1-2 Incidence of Intubation for Any Reason within 72 Hours of Life (nCPAP Failure) in Study 03-CL-1201.

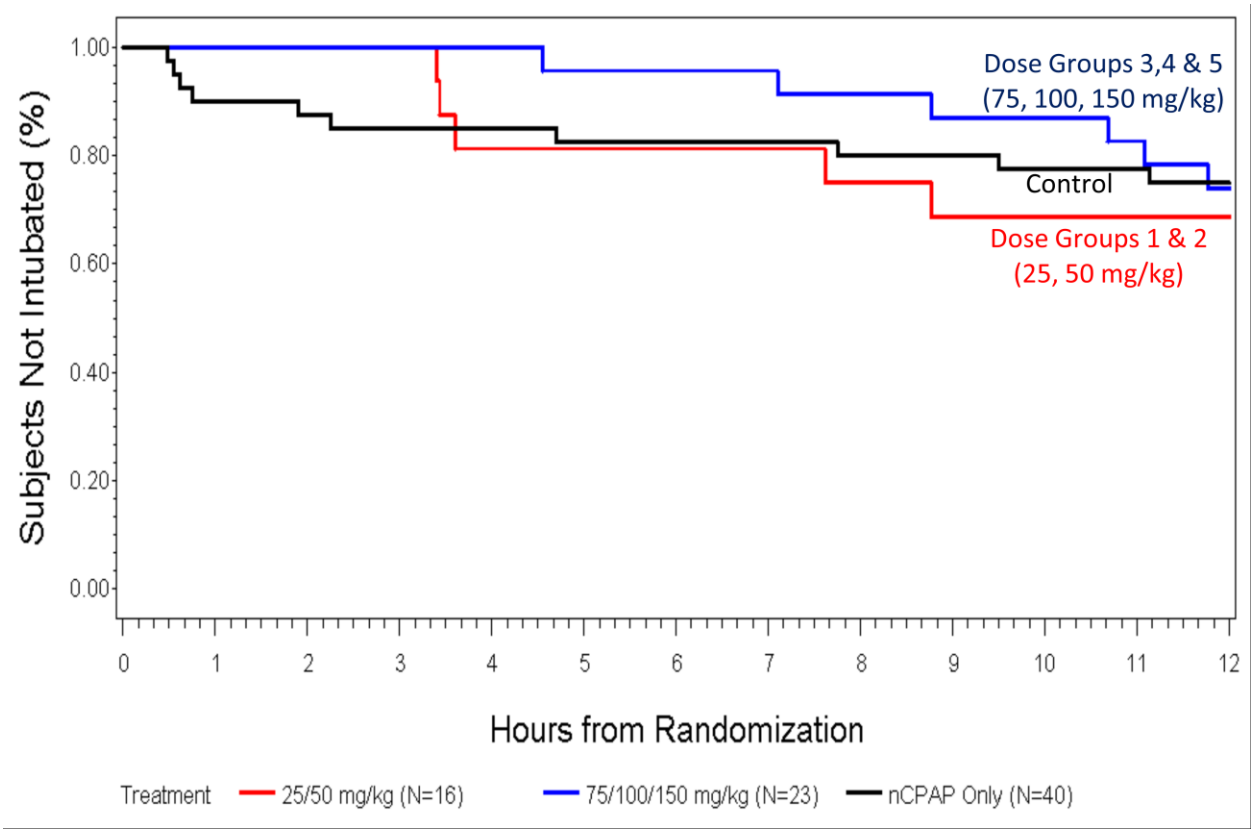

Figure 1-3 Kaplan-Meier plot showing proportion of subjects not intubated over the first 12 hours after randomization into Study CL-03-1201. The higher 3 dosage groups (blue line) and lower 2 dosage groups (red line) are shown combined, vs all controls (black line).

In conclusion, the results from Study 03-CL-1201 demonstrate that delivery of lucinactant as an aerosol using the ADS is feasible and that lucinactant for inhalation appears to be generally well-tolerated in infants 29-34 weeks PMA with RDS. Exploratory assessment of clinical efficacy parameters suggests that lucinactant for inhalation may be providing beneficial effects.

1.3.2.2 Study 03-CL-1401

Study 03-CL-1401 is a Phase 2a, multicenter, randomized, open-label, controlled dose-escalation study assessing the safety and tolerability of aerosolized lucinactant delivered using the ADS in preterm infants 26 to 28 completed weeks PMA. The planned intent is to evaluate the safety of up to 4 dose-exposures of aerosolized lucinactant in conjunction with nCPAP: 50 mg TPL/kg, 75

mg TPL/kg, 100 mg TPL/kg and 150 mg TPL/kg. One repeat dose is possible for all dosages. Neonates treated with nCPAP alone serve as the control group. A total of 22 study sites from the US, Canada, Poland and Chile have received IRB/REB/EC, health authority approval, where applicable, and sponsor approval for participation in the study.

As of the data cut-off date for this Amendment (21 Feb 2017), 45 subjects have been enrolled, with 8 each in the 50 and 75 mg TPL/kg groups, 6 in the 100 mg TPL/kg group, and 23 in the control group; the 150 mg TPL/kg group is not yet open for enrollment. Active and control subjects have been similar in terms of gestational age, birth weight, gender, race and ethnic origin. All active subjects received at least one treatment, and 15 (68%) received a repeat treatment. Median time to initiation of study treatment was 5.3 hours after birth.

Study drug treatment (initial or repeat) was discontinued early in 9 (41%) subjects: 8 (36%) due to "device failure or malfunction" and none due to signs of acute respiratory deterioration or investigator judgment. Most (5/8, 63%) of the device errors have been due to a "syringe pressure out of range" error, which likely resulted from micro-occlusions within the filter in the ADP, predominantly with certain manufacturing lots. When such errors occurred, supplemental lucinactant for inhalation was administered according to a schedule such that subjects received 90-110% of the intended dosage.

To date, the incidence of AEs and common complications of prematurity have been as expected for this population. AEs have been comparable between treatment and control groups, occurring in all active and control subjects. The 3 most common AEs have been neonatal apnea (occurring in 15 [68%] active and 17 [74%] control subjects), neonatal anemia (12 [55%] active and 9 [39%] controls), and neonatal jaundice (9 [41%] active and 12 [52%] controls). The 3 most common complications of prematurity were apnea (16/22 [73%] active and 15/23 [65%] controls), PDA (10/22 [45%] active and 6/23 [26%] controls), and acquired sepsis (6/22 [27%] active and 3/23 [13%] control subjects). The small numbers of subjects in each group makes comparisons of these preliminary data difficult, but to date incidences appear to be generally comparable. Peri-dosing events have been uncommon, occurring in 7 (32%) active subjects with no clear increase in incidence as dosage has increased. The 3 most common peri-dosing events have been desaturation in 6 (27%) subjects, bradycardia in 3 (14%) subjects, and apnea in 3 (14%) subjects. SAEs have occurred in 9 (41%) of active subjects, with no increase in incidence as dosage has increased, and 6 (26%) of control subjects. Lucinactant for inhalation has had no clinically important effect on serum electrolytes, gastric liquid volume, or defecation.

Air leaks have occurred in 4 (18%) active subjects and 2 (9%) control subjects (Table 1-2). Two of the subjects in the 50 mg TPL/kg group who experienced air leaks are twins who were subsequently diagnosed with Ehlers-Danlos syndrome, a genetic connective tissue disorder in which spontaneous pneumothorax in children can be a presenting sign.

Table 1-2: Air Leaks Reported as Adverse Events in Study 03-CL-1401

	50 mg TPL/kg (N=8)	75 mg TPL/kg (N=8)	100 mg TPL/kg (N=6)	150 mg TPL/kg (N=–)	Total Active (N=22)	nCPAP Only (N=23)
Number of Subjects with an Air Leak[1]	3 (38%)	0	1 (17%)	—	4 (18%)	2 (9%)
Pneumothorax	1 (13%)	0	1 (17%)	—	2 (9%)	1 (4%)
PIE	2 (25%)	0	0	—	2 (9%)	1 (4%)

[1] Subjects may have had more than one type of air leak

PIE = pulmonary interstitial emphysema

After enrollment in each dosing group of Study 03-CL-1401 was completed, the Safety Review Committee (SRC) reviewed all safety data as specified in the study protocol. No findings of concern were identified, and the study was allowed to proceed to subsequent dosing groups. In addition, the SRC agreed that neonates 26-28 weeks PMA could be enrolled in the present study (Study 03-CL-1202).

Study 03-CL-1401 was neither designed nor powered to investigate efficacy. However, clinical parameters associated with efficacy (and safety) were measured. Preliminary results are described here for completeness and to inform dosage selection for Part B of the present study (see Section 2.2.3).

To date, active subjects have been no different from controls in change in FiO_2 or PCO_2 or in incidence of intubation within 72 hours of life (Figure 1-4). The reason for this apparent lack of effect is uncertain. As a safety study, Study 03-CL-1401 is not powered to detect efficacy so it may simply be too small to detect any difference in efficacy parameters, particularly since the likelihood of intubation in general rises with lower GA. Both active and control subjects were much more likely to be intubated if their baseline FiO_2 was ≥0.35 (10/11 [91%] active and 9/9 [100%] controls) vs <0.35 (7/12 [58%] active and 6/14 [43%] controls), suggesting that subjects whose baseline FiO_2 was ≥0.35 were highly likely to be intubated regardless of treatment assignment. As a dose-escalation study, it is also possible that an effective dosage has not yet been reached, particularly since RDS is more common and often more severe in this immature

population than in neonates 29-34 weeks PMA, suggesting that they have a greater deficiency of surfactant and would require a higher dosage. Finally, since the literature supports administering SRT as early as possible especially in extremely preterm neonates (2-6), it is possible that the time between birth and treatment (5.3 hours) and the interval between treatments (4.6 hours) reduced the effectiveness of the treatment. This is supported by the observation that intubation occurred somewhat later in active patients vs controls (Figure 1-5).

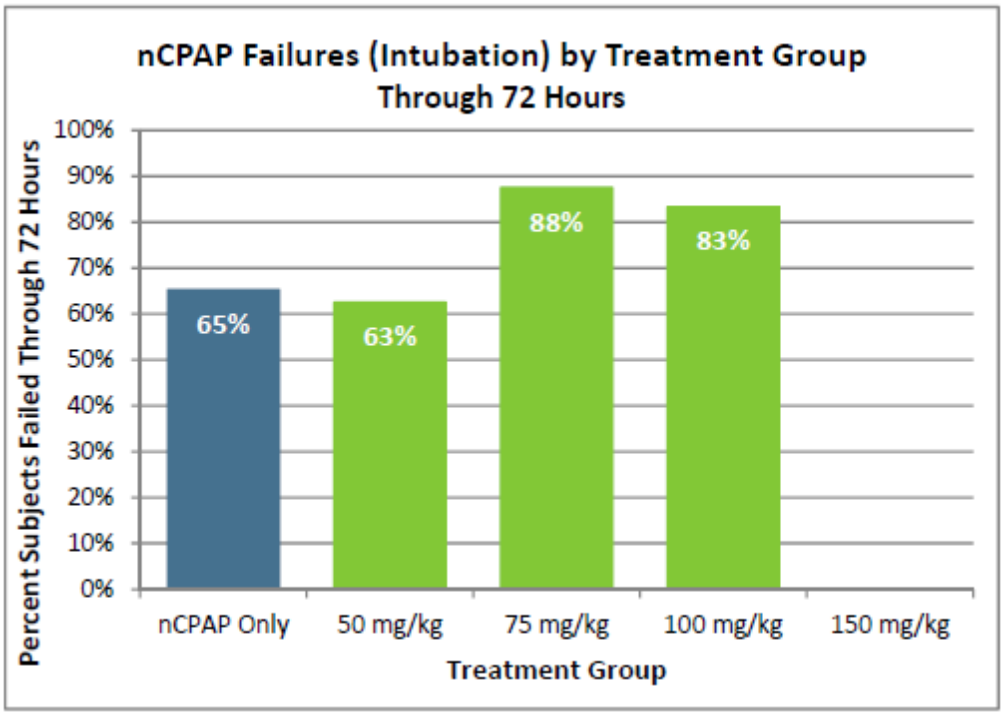

Figure 1-4. Incidence of Intubation for Any Reason within 72 Hours of Life (nCPAP Failure) in Study 03-CL-1401.

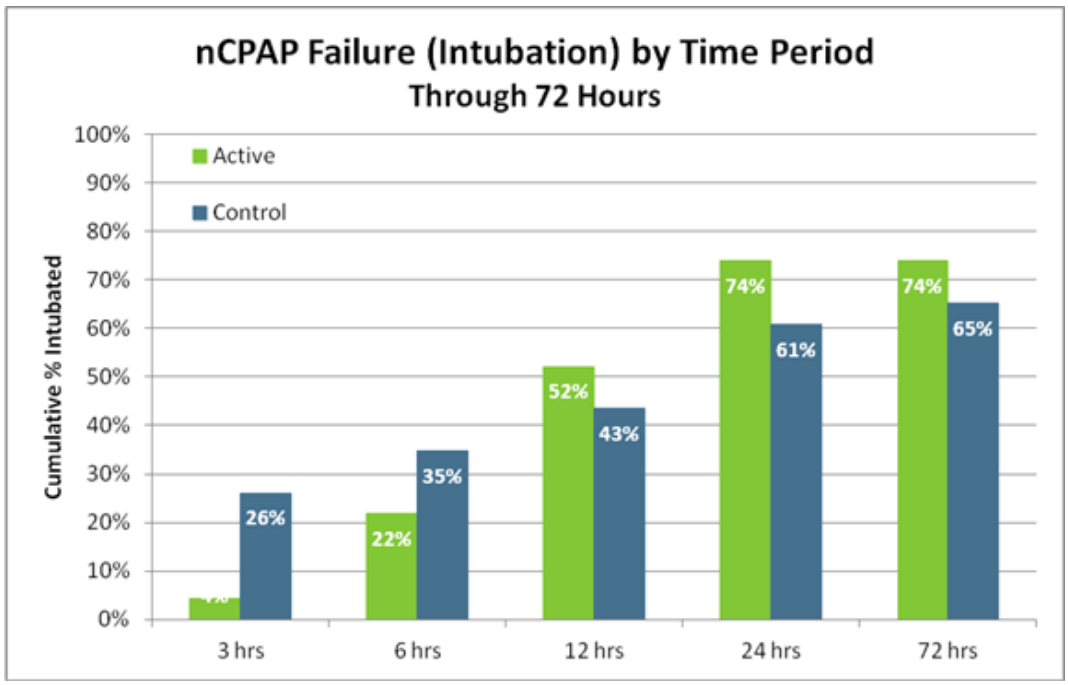

Figure 1-5: Time to Intubation for Any Reason within 72 Hours of Life (nCPAP Failure) in in Study 03-CL-1401.

In conclusion, the preliminary results from Study 03-CL-1401 to date demonstrate that delivery of lucinactant as an aerosol using the ADS is feasible and that lucinactant for inhalation appears to be generally well-tolerated in infants 26-28 weeks PMA with RDS. Although the study is not powered for efficacy, it is likely that a total dosage greater than 100 mg TPL/kg (repeated more than 1 time) is required in this population.

2 STUDY DESIGN AND RATIONALE

This study will investigate the safety and efficacy of lucinactant for inhalation in conjunction with nCPAP compared to nCPAP alone. The study design is broken into 2 sequential parts. Part A will be masked and include neonates 28 to 32 completed weeks PMA. Part B will commence after completion of Part A, will include neonates 26 to 28 completed weeks PMA, and will be open-label. Part A will include 2 dosages of lucinactant for inhalation in 3 parallel treatment groups (40 mg TPL/kg lucinactant for inhalation, 80 mg TPL/kg lucinactant for inhalation, and nCPAP only; initial single dose with up to 2 repeat doses) in preterm neonates 28 to 32 completed weeks PMA with RDS who are within the first 20 hours after birth, who had successful implementation of non-invasive support or ventilation within 90 minutes of birth, and who are candidates for SRT. Part B will include 1 dosage of lucinactant for inhalation in 2 parallel treatment groups (80 mg TPL/kg lucinactant for inhalation and nCPAP only; single dose with up to 4 repeat doses) in preterm neonates 26 to 28 completed weeks PMA with RDS who are within the first 12 hours after birth, who had successful implementation of non-invasive support or ventilation within 60 minutes of birth, and who are candidates for SRT.

2.1 Study Design

This study is a sequential 2-part, multinational, multicenter, masked (Part A)/open-label (Part B), randomized, controlled study to evaluate the safety and efficacy of lucinactant for inhalation in conjunction with nCPAP compared with nCPAP alone, in preterm neonates 28 to 32 completed weeks PMA (Part A) and in preterm neonates 26 to 28 completed weeks PMA (Part B). There will be 2 phases in Parts A and B of the study: a primary phase through 36 weeks PMA and a longer-term follow-up phase through 1-year corrected age. Data will be analyzed and reported at the completion of each respective study phase for Parts A and B of the study.

Before study enrollment, parents or legal guardians will provide a signed written 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.

For Part A of the study, inclusion criteria to be met within the first 20 hours after birth include respiratory insufficiency with a requirement for nCPAP of 5 to 7 cm H_2O and a fraction of inspired oxygen (FiO_2) ≥0.25 (>0.21 for neonates 28 weeks PMA) to 0.4 to maintain oxygen saturation measured by pulse oximetry (SpO_2) of 90% to 95% for at least 30 minutes. For Part B of the study, inclusion criteria to be met within the first 12 hours after birth include respiratory insufficiency with a requirement for nCPAP of 5 to 7 cm H_2O with a FiO_2 >0.21 to 0.4 to maintain SpO_2 of 90% to 95% for at least 20 minutes. As soon as study qualification has been confirmed and the informed consent is signed, subjects will be immediately randomized to an active treatment group (2 active groups in Part A; 1 active group in Part B) or the control (nCPAP only, with simulated ["sham"] study drug treatment in Part A) group. Subjects in Part A will be enrolled by strata: approximately 5-10% (12-24) of the subjects will be 28 completed weeks PMA and approximately 206-228 of the subjects 29 to 32 completed weeks PMA. Randomization in Part B will be stratified by treatment within each gestational age (26, 27, and 28 completed weeks PMA) and up to 80 patients will be enrolled. Study therapy (lucinactant for inhalation or sham/control) must be initiated as soon as possible after randomization. Treatment groups are outlined in Section 5.5.

In Part A, subjects may be eligible to receive up to 2 repeat doses of the treatment to which they are assigned. Repeat doses will be given as soon as 2 hours from completion of the previous dose up to 36 hours after completion of randomization if subjects meet repeat dosing criteria, unless it is unsafe to do so in the judgment of the investigator, as described in Section 5.7. Should this situation arise the investigator will document the circumstances in the eCRF. Subjects randomized to a control group will be continued on nCPAP alone but will receive repeated sham treatment to maintain study masking.

In Part B, subjects in the active group may be eligible to receive up to 4 repeat doses of the treatment to which they are assigned. Repeat doses will be given as soon as 30 minutes from completion of the previous dose up to 36 hours after completion of randomization if subjects meet repeat dosing criteria, unless it is unsafe to do so in the judgment of the investigator, as described in Section 5.7.

In both parts of the study, all subjects in the active treatment groups will receive the same drug concentration of lucinactant for inhalation (30 mg TPL/mL) at the same rate of delivery (aerosolized concentration of 4.2 mg TPL/L in aerosol carrier gas flow of 3 L/min). The dosage will vary by the predetermined administration time for each dose. Lucinactant for inhalation will be delivered by the investigational ADS device in conjunction with a commercially available

nCPAP generator and patient interface. Details on dosage calculations and rationale are given in Section 2.2, and the drug delivery device is outlined in Section 5.1.

In Part A, treatment assignments will be masked from the principal investigator (PI), clinical and study staff (eg, site coordinator, bedside nurse), as applicable; sponsor, as applicable; and subject's parents/legal guardians. In Part B, treatment assignments will be open-label.

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.

In both parts of the study, neonates will be followed for the primary phase efficacy and safety evaluations through 36 weeks PMA, NICU 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 followed up to 1-year corrected age, at which time a physical examination will be performed, including an abbreviated neurologic assessment. (See also Sections 7 and 8.)

A schematic diagram of the study design is displayed in Figure 2-1.

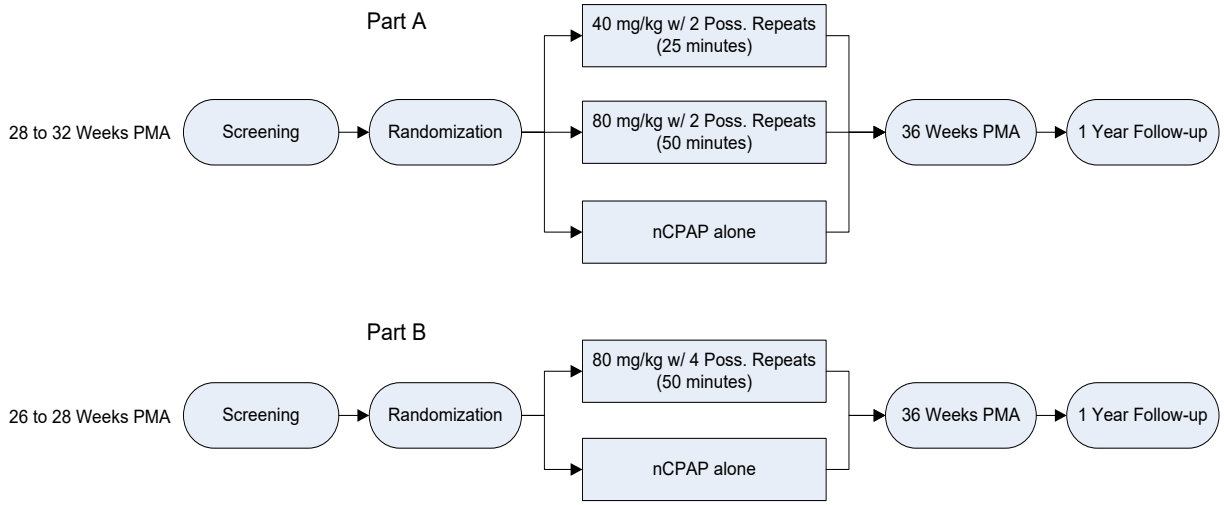

Figure 2-1 Schematic of Study Design for 03-CL-1202

2.2 Dose and Device Description and Rationale

In Part A of this study, up to 160 subjects (up to 80 in each of the 2 lucinactant for inhalation treatment groups) and in Part B up to 40 subjects will be randomized to an active treatment group and will receive aerosolized lucinactant through the ADS in conjunction with nCPAP. Up to 80 subjects in Part A and up to 40 in Part B will be randomized to the control group and will receive nCPAP alone with "sham" study drug treatment.

2.2.1 General Description and Rationale for the ADS

A full description of the ADS is given in Section 5.1. 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.

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.

2.2.2 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 allow 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 (3-6, 11).

Initial treatment with brief intubation, surfactant delivery and extubation (the "INSURE" technique) or other forms of 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 5.2.1) 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 for the blinded Part A while continued nCPAP is the appropriate control for the open-label Part B.

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 therefore ethical to administer for initial or repeat dosing.

2.2.3 Dosage Rationale

2.2.3.1 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, 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, prenatal steroids, etc. 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 1.3.1) 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. Preclinical studies in animal models of RDS (28) and acute lung injury (29) suggest that the effective dosage of aerosolized surfactant may be as little as 5% that of the effective dosage of intratracheal surfactant. Thus, it is likely that preterm neonates on nCPAP will require substantially less than the intratracheal bolus dose of 175 mg TPL/kg of lucinactant.

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 (30) but with similar physiologic effects (31).

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 (32, 33), 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. When lucinactant was aerosolized using the ADS and delivered via nCPAP (5 cmH_2O) to cynomolgus macaques, whose airway anatomy is similar to that of preterm human neonates, the inhaled dose was deposited homogenously throughout the lungs (34).

2.2.3.2 Calculation of the Theoretical Inhaled Dose

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. 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 dose can be estimated using the following equation:

$$\text{Inhaled Dose} = C \times \left({}^{Vm}/_{kg} \right) \times T \qquad \textit{Equation 1}$$

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)

All of the lucinactant that flows through the CAG is aerosolized; however, since much of the aerosolized drug impacts within the aerosol tubing only 35% reaches the patient interface. The emitted dose rate of the ADS is therefore the product of the flow rate of lucinactant through the CAG (1.2 mL/min), the concentration of the reconstituted lucinactant in the dosing syringe (30 mg TPL/mL) and the fraction of the aerosolized dose that is reaches the patient interface (35%) (see Investigator's Brochure for further information):

Emitted dose rate = 1.2 mL/min × 30 mg TPL/mL × 0.35 = 12.6 mg TPL/min *Equation 2*

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 (33, 35). The concentration of aerosolized lucinactant in the carrier gas (C) is therefore the emitted dose rate (12.6 mg TPL/min) divided by the carrier gas flow rate (3 L/min).

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

Minute ventilation (Vm) of preterm neonates can be estimated based on body weight, as shown in Table 2-1 (32, 33). 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 2-1. Estimated Minute Ventilation of Preterm Neonates, by Weight

	Bide et al. (32)		Bhutani et al. (33)	
	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

The time required to deliver the desired dose (T) can therefore be calculated by rearranging *Equation 1* in terms of T; that is, dividing the desired theoretical inhaled dose by the product of C (4.2 mg TPL/L) and Vm (0.4 L/min/kg). For example, this calculation yields dose durations of 50 minutes to achieve a target theoretical inhaled dose of 80 mg TPL/kg and 90 minutes for a dose of 150 mg TPL/kg.

2.2.3.3 Rationale for Dosages Used in the Current Study

The dosages used in completed study 03-CL-1201 were 25, 50, 75, 100 and 150 mg TPL/kg and in ongoing study 03-CL-1401 to date have been 50, 75, and 100 mg TPL/kg. From the practical standpoint, however, a dosage > 80 mg TPL/kg is cumbersome to administer. Two lucinactant

syringes of 60 mL each are required for these higher dosages, and the ADS system must be temporarily shut down during administration in order to change the syringe.

To improve the practical viability of the program, Discovery has decided to develop and evaluate dosages of 40 and 80 mg TPL/kg. The higher dosage is the largest dosage that can be practically administered with a single 60 mL syringe. Using the dosage calculation in Section 2.2.3.2, the dosing durations for the 40 mg TPL/kg and 80 mg TPL/kg dosages would be 25 and 50 minutes, respectively. Dosages are approximate, as each neonate's minute ventilation and pulmonary characteristics may vary slightly. If higher dosages are necessary, this can be achieved with repeat dosing, as is frequently done with intratracheal surfactant administration (1). Part A of this study will evaluate both dosages, while Part B will use only the 80 mg TPL/kg dosage.

2.2.3.4 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 for the highest possible dose in Part A (240 mg TPL/kg) and > 6.75:1 for the

highest possible dose in Part B (400 mg TPL/kg), whether delivered to the lungs (> 2700 mg TPL/kg) or swallowed (8400 mg TPL/kg) (including volume load and sodium load).

2.2.3.5 Clinical Experience Supporting Dose Rationale

In neonates 28-34 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 1.3.2 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 hrs of life vs 53% of pooled controls (Figure 1-2). 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 2-2, Figure 2-3). 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 2-4). These results suggest 80 mg TPL/kg dosage is likely to be effective.

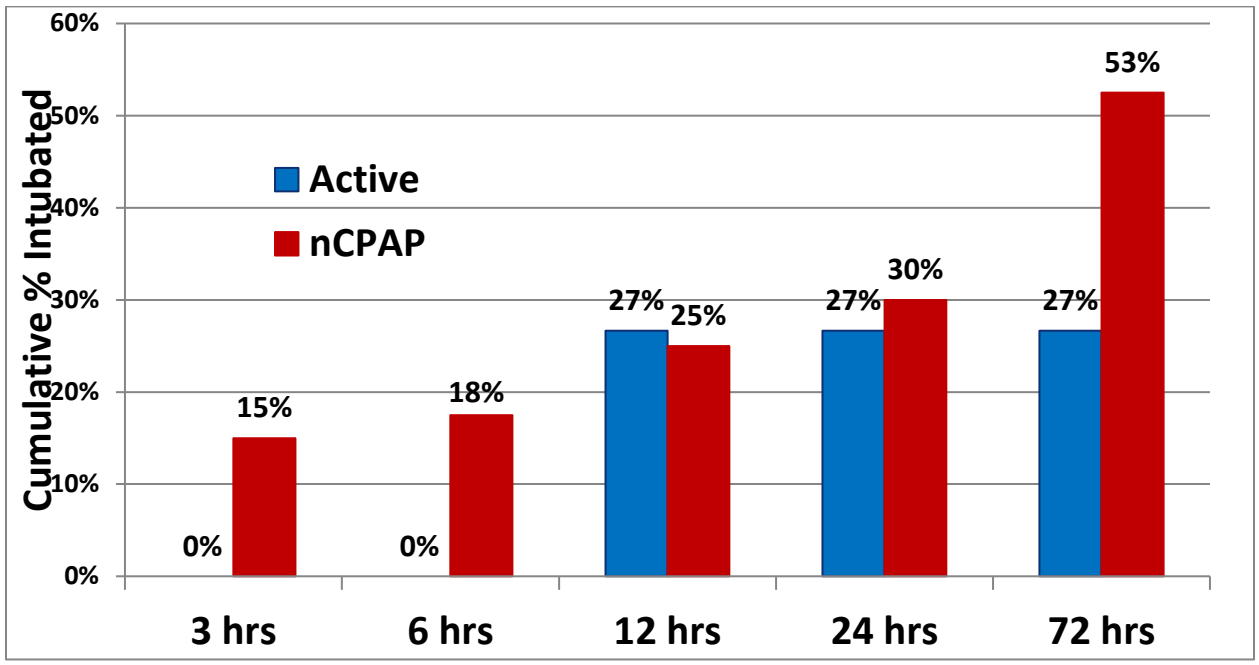

Figure 2-2: Cumulative incidence of intubation for any reason within 72 hours of life (nCPAP Failure) in Study 03-CL-1201 among subjects receiving lucinactant for inhalation 75 or 100 mg TPL/kg, by treatment group.

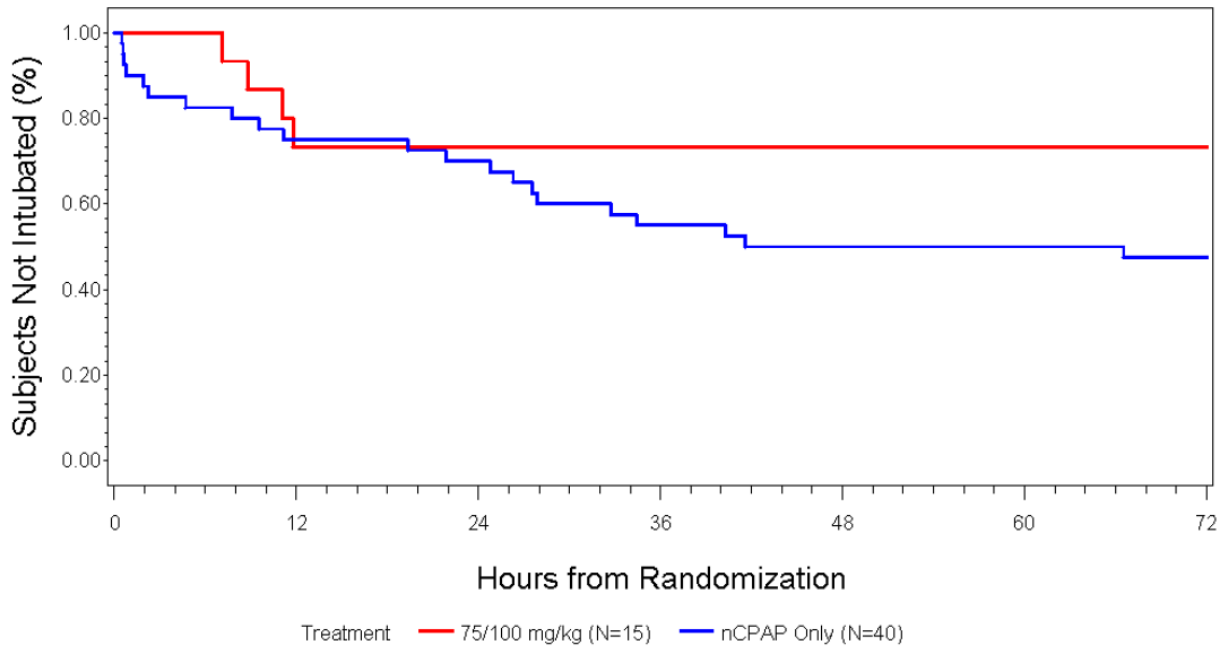

Figure 2-3: Kaplan-Meier plot showing proportion of subjects not intubated over the first 12 hours after randomization into Study CL-03-1201. Dosages of 75 and 100 mg TPL/kg are shown combined (red line), vs all controls (blue line).

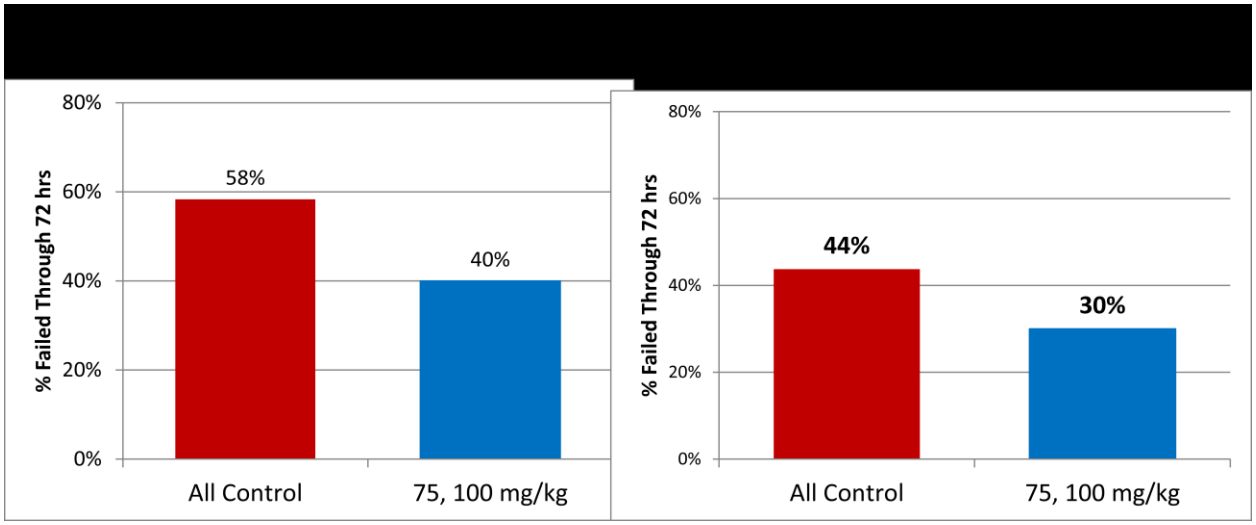

Figure 2-4: Incidence of intubation for any reason within 72 hours of life (nCPAP Failure) in Study 03-CL-1201 among subjects receiving lucinactant for inhalation 75 or 100 mg TPL/kg, by gestational age group and by treatment group.

In neonates 28-34 weeks PMA, outcomes with a dosage of 40 mg TPL/kg can be estimated by looking at results from subjects receiving the minimum dosage (25 mg TPL/kg) in Study 03-CL-1201. AEs, SAEs and complications of prematurity occurred in this group at a rate similar to that of the remainder of the active cohort and controls, suggesting 40 mg TPL/kg would be well-tolerated. FiO_2 was observed to fall more quickly in this group than in controls (Figure 2-5), suggesting a positive physiological effect on lung compliance. The rate and timing of nCPAP failure was not observed to be different in this group from control; however, the study was not powered for efficacy evaluations. Repeat treatment of each dosage will also be available for each subject, which may improve efficacy at this dosage. Taken together, these results suggest the 40 mg TPL/kg dosage is likely to be well-tolerated and to have the potential for efficacy, particularly with the ability to provide repeat doses.

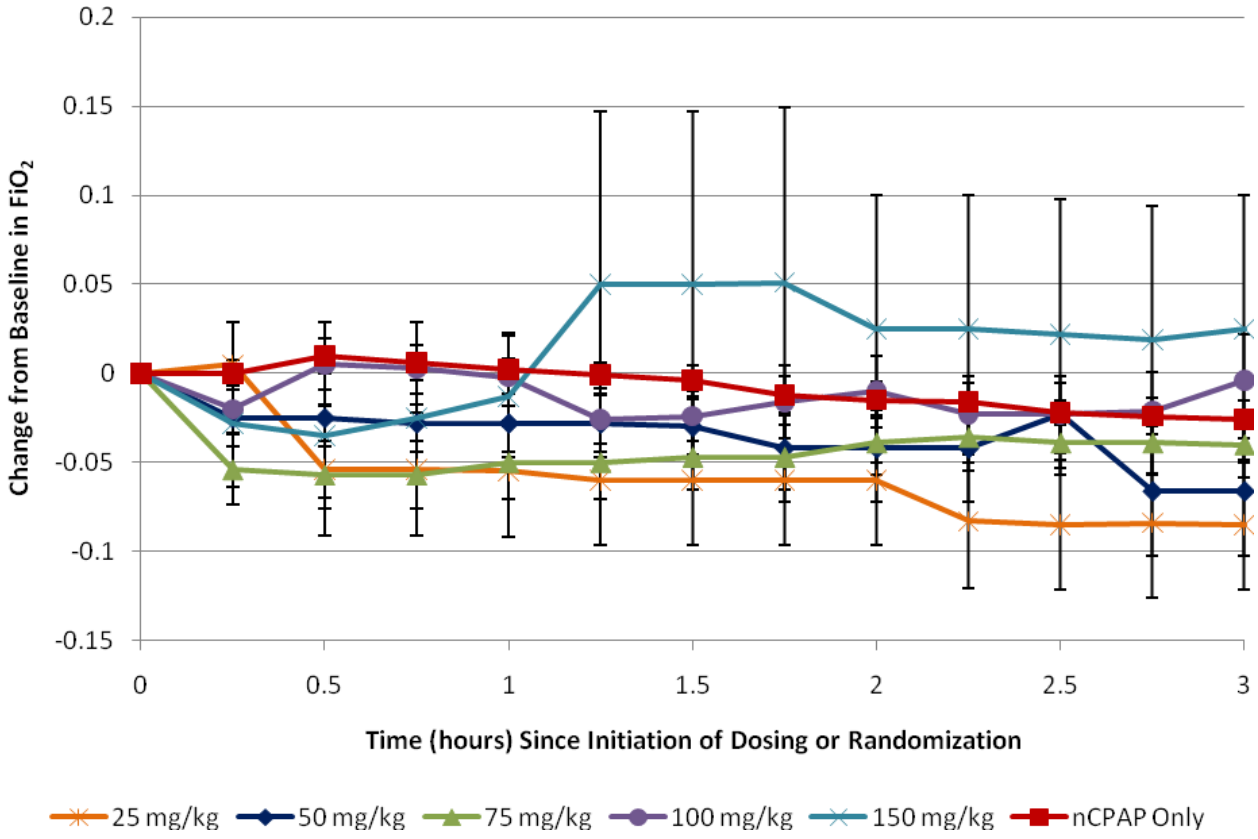

Figure 2-5: Change from baseline in FiO_2 of all subjects in Study 03-CL-1201, by treatment. Subjects receiving 25 mg TPL/kg are shown in orange vs control subjects in maroon.

In neonates 26-28 weeks PMA, preliminary results from Study 03-CL-1401 are relevant. In this study, dosages up to 100 mg TPL/kg with a possible repeat dose have been administered. AEs, SAEs and complications of prematurity have occurred at rates in the active groups similar to the remainder of the active cohort and controls, suggesting that repeated doses of 80 mg TPL/kg would be well-tolerated. To date, nCPAP failure at 72 hours of life has occurred at a similar rate in active and control subjects even at the 100 mg TPL/kg dosage, but tends to occur later in active patients (Figure 1-5). There are several possible explanations for this observation (see Section 1.3.2.2), but the likelihood is that the dosages delivered to neonates 26-28 wks PMA in Study 03-CL-1401 have been inadequate to compensate for their greater surfactant deficiency relative to neonates 29-32 wks PMA. In addition, the observation that intubation in active

subjects occurred later than in controls in both Study 03-CL-1401 (Figure 1-5) and Study 03-CL-1202 (Figure 2-2) suggest that lucinactant for inhalation may delay respiratory failure, raising the possibility that earlier and more frequently repeated doses may hold off respiratory failure until neonates begin manufacturing endogenous surfactant, which is the natural course of RDS. For this reason, Part B of this study focuses on administration of lucinactant for inhalation which begins as early and is repeated as often as practically possible, with as short a time between repeated doses as practically possible.

Limited additional inferences can be made from prior clinical studies in which lucinactant was administered using aerosol generators other than the ADS or through non-aerosol administration. A prior clinical study of aerosolized lucinactant (Study KL4-CPAP-01) (27) using a commercially-available vibrating mesh nebulizer generated a theoretical inhaled dose of approximately 72 mg TPL/kg over a 3-hour period for RDS prophylaxis in preterm neonates 28 to 32 weeks PMA (Section 1.3.1). In this cohort of 17 neonates, 5 (30%) required intratracheal SRT, suggesting that the dosage used may be efficacious.

Subjects in Part A of this study may receive up to 2 repeat doses, and those in Part B may receive up to 4 repeat doses. Thus, the subjects in the 80 mg TPL/kg group of Part A could receive a total of 240 mg TPL/kg over approximately 6 to 36 hours, and active subjects in Part B could receive a total of 400 mg TPL/kg over a somewhat shorter interval. Repeated doses of intratracheal surfactant are often necessary and beneficial in neonates with RDS (1). In study 03-CL-1201 (Section 1.3.2.1), 3 subjects received repeated doses: 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). In Study 03-CL-1401 (Section 1.3.2.2), 2 total doses of up to 100 mg TPL/kg (total dosage of 200 mg TPL/kg) have been administered over approximately 6 hours and have been well-tolerated. 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 doses (total dose of 700 mg TPL/kg) over 24-48 hours, each of which is administered over a few minutes. In addition, neonates with meconium aspiration syndrome have received doses of Surfaxin® 120 mg TPL/kg (36) 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 (37). Thus, dosages administered in both Parts A and B of this study are well within the FDA-approved dosage of intratracheal lucinactant.

2.2.4 Risk and Benefit of Study Interventions

Risks and benefits of this study must be considered within the context of treating RDS in preterm infants (Section 1.1), which carries with it substantial risk of morbidity and mortality. These infants often require intratracheal SRT as well as MV in order to survive; however, both MV and endotracheal intubation are themselves associated with morbidity and mortality in this fragile population. Various types of non-invasive support and 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, ROP, IVH and NEC.

2.2.4.1 *Risk and Benefit of Control Treatment*

As described in Section 5.4.2, control treatment in Part A of this study involves continuing subjects on nCPAP while the ADS is delivered to the bedside (in a blinded fashion) but is not used ("sham" treatment), and in Part B involves continuing nCPAP alone. Thus, control/sham treatment in both Part A and B of the study is identical to standard therapy with nCPAP. As described in Section 2.2.2, 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 1.1.1). The risk of requiring endotracheal intubation and SRT has been reported as 33-67% (Section 1.1.1). Risks of nCPAP in the prior clinical study using the ADS (Study 03-Cl-1201, Section 1.3.2) 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 1.1.1).

2.2.4.2 *Risk and Benefit of Active Treatment*

Because the ADS delivers lucinactant for inhalation via conventional nCPAP (Section 5.6), active treatment would include the same risks and benefits of respiratory support with standard

nCPAP therapy described above in Section 2.2.4.1. Active treatment would carry the additional risks and benefits of aerosolized SRT with lucinactant for inhalation.

Lucinactant for inhalation is the reconstituted form of a lyophilized liquid surfactant (Surfaxin® [lucinactant]); 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® Product 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 the prior clinical study using aerosolized lucinactant for inhalation via the ADS (Study 03-CL-1201, Section 1.3.2), 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 are continuously attended by a qualified clinician during dosing and are continuously monitored for oxygen saturation (SaO_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 (Section 5.1). 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 ongoing study 03-CL-1401, the incidence of AEs has been similar in subjects receiving active treatment compared to controls and has been as expected for this population of preterm neonates. The 3 most common AEs have been neonatal apnea, anemia and jaundice, and neither upper airway obstruction nor serious peri-dosing events have been observed. Risk of air leak has been lower than in Study 03-CL-1201: 18% in active subjects and 9% in controls. Automatic shutdown of the ADS has occurred in 41% of subjects; as with Study 03-CL-1201, most shutdowns resulted from error codes, and none resulted in loss of nCPAP or in any AE being reported related to the shutdown. The cause of one type of error code has been identified (syringe pressure out of range, mainly in certain ADP lots), and a corrective action has been undertaken (addition of a pre-filter for these lots of ADPs; see Investigator's Brochure for details) in regions where these ADP lots have been distributed.

2.2.4.3 *Alternatives to Study Treatment*

Alternative approaches to treating neonates with (or at risk for) RDS, as described in Sections 1.1 and 2.2.2, include attempting to support the neonate solely with a form of NIV (possibly 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 2.2.4.1 above, the former 2 approaches are identical to control treatment in the present study. Each of these approaches is supported by international guidelines (3-6, 11), and no strategy has yet been demonstrated as being superior in neonates who do not require immediate intubation.

2.2.4.4 Summary of Risk-Benefit Assessment

In summary, the potential benefit of lucinactant for inhalation 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.

2.3 Study Duration

It is expected that recruitment will occur over a period of approximately 18 to 20 months for the sequentially conducted Part A and Part B of the study. It is estimated that the last subject enrolled will complete all assessments and procedures within approximately 20 to 22 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 6).

2.3.1 Duration of Subject Study Participation

The total duration of study participation for each subject in the primary phase of both Parts A and B of the study will be from enrollment (≤ 20 hours from birth) to 36 weeks PMA. Each subject will participate in a follow-up phase through 1 year corrected age (1 year after the subject reaches 40 weeks PMA). All subjects who die or who complete all assessments and procedures up to and including the Final Observation (to occur at 36 weeks PMA or NICU 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 8):

Primary Phase:

- Screening Period: To occur in a timely manner to allow for study randomization ≤ 20 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.
  - Where permitted by the local ethics committee, consent may be obtained prenatally
- Primary Observation Period: Time of randomization (T_0 on study) to 72 hours (Day 3) from randomization.
- Extended Observation Period: ≥ Study Day 4 to completion on Study Day 7 (6 days after the day of randomization by calendar date).
- Final Observation Period: ≥ Study Day 8 to Final Visit at 36 weeks PMA, NICU discharge, death, or hospital transfer (whichever occurs first).

Longer-Term Follow-Up Phase:

- Longer-Term Follow-Up Period: Evaluations occur at 6 months and 1 year corrected age.

3 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 and 03-CL-1401 to allow for potential comparison and pooling of results.

3.1 Objectives

To evaluate the safety and efficacy of lucinactant for inhalation in conjunction with nCPAP, compared to nCPAP alone, in preterm neonates with RDS, as assessed by the time to and incidence of respiratory failure and/or death due to RDS over the first 72 hours of life, the incidence of BPD at 36 weeks PMA, and change in physiologic parameters (FiO_2 and PCO_2) over the first 72 hours of life.

3.2 Efficacy Endpoints

3.2.1 Primary Endpoint

The primary endpoint for this study is the incidence of respiratory failure or death due to RDS within the first 72 hours of life.

A subject will be categorized as having respiratory failure due to RDS if either of the following occur:

1. Intubation for MV and/or surfactant administration (with or without MV) within 72 hours of life, including SRT techniques such as INSURE, LISA and MIST
2. The subject meets at least 1 of the following criteria, regardless of whether endotracheal intubation is performed:
    a. A sustained (≥ 60 minutes) need for $FiO_2 > 0.45$ to maintain an $SpO_2 > 90\%$ to 95%
    b. A sustained (on ≥ 2 consecutive observations > 60 minutes apart) transcutaneous $PCO_2 > 65$ mm Hg
    c. nCPAP > 8 cm H_2O

Death due to RDS is any death whose primary cause is respiratory failure due to RDS.

Respiratory failure due to RDS will be categorized as follows:

- Respiratory failure, early — Respiratory failure occurring ≤ 72 hours after birth
- Respiratory failure, late — Respiratory failure occurring > 72 hours and ≤ 7 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 Appendix 2 until the time the subject completes the study or withdraws (Section 10.2).

3.2.2 Secondary Endpoints

The secondary endpoints of this study include the evaluation of the following from the time of initiation of study treatment until study completion:

1. Time to respiratory failure or death due to RDS
2. Incidence rate of BPD at 36 weeks PMA (defined in Appendix 1)
3. All-cause mortality
4. Incidence rate of survival without BPD at 36 weeks PMA
5. Incidence rate of air leak (defined in Section 9)

3.2.3 Tertiary Endpoints

The tertiary endpoints of this study include the evaluation of the following from the time of initiation of study treatment until study completion:

1. Incidence rates of common complications of prematurity other than air leak (defined in Section 9)
2. Change from baseline in FiO_2 and/or transcutaneous PCO_2 over the first 72 hours of life

3.3 Safety Endpoints

The following safety measures are to be documented in the electronic case report form (eCRF) in accordance with timings outlined in Appendix 2 and Section 8:

1. Survival (date and time of death, if applicable)
2. AEs, including adverse device effects (ADEs) and AEs of special interest including peri-dosing events, complications related to placement of bi-nasal prongs, and air leak (Section 9)

3. Concomitant medications (Section 7.3)
4. Use of respiratory support and supplemental O_2 (Section 7.5), including the following:
    a) Need for endotracheal intubation and MV
    b) Mode of respiratory support (including supplemental oxygen) and important parameters for that mode (Section 7.5.5)
5. Complications of prematurity (Section 9)
6. Physical examinations (Section 7.1.6)
7. Tolerability of lucinactant for inhalation
8. Incidence of air leak (Section 9)
9. Assessments of the following:
    a) Vital signs (Section 7.1.1)
    b) O_2 saturation, as determined by pulse oximetry (SpO_2) (Section 7.1.3)
    c) Serum electrolyte measurements (Section 7.1.7)
    d) Defecation (Section 7.1.9)
    e) Chest radiography prior to intubation (Section 7.1.8)

4 STUDY POPULATION SELECTION

This study is anticipated to enroll in Part A up to 240 preterm neonates (up to 80 per treatment group) 28 to 32 completed weeks PMA who are candidates for SRT and nCPAP in a NICU setting, and in Part B up to 80 preterm neonates (up to 40 per treatment group) 26 to 28 completed weeks PMA who are candidates for SRT and nCPAP in a NICU setting.

4.1 Study Population

This study population will be comprised of preterm neonates 26 to 32 completed weeks PMA who are receiving care in a NICU and are receiving nCPAP as the primary support modality for RDS. Part A of the study will enroll neonates 28 to 32 completed weeks PMA by strata: subjects 28 completed weeks PMA will be defined as one stratum and subjects 29 to 32 completed weeks PMA will be defined as the other stratum. Part B of the study will enroll neonates 26 to 28 completed weeks PMA, and will be stratified by treatment within each completed week PMA (26, 27, and 28 completed weeks PMA).

The study population for Part A will be randomized in a 1:1:1 ratio into 1 of 3 treatment groups and the population for Part B will be randomized in a 1:1 ratio into 1 of 2 treatment groups (see Section 5.4).

4.2 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 (consent may be obtained prenatally, where allowed)
2. Gestational age:
    a) Part A: 28 0/7 to 32 6/7 completed weeks' gestation PMA
    b) Part B: 26 0/7 to 28 6/7 completed weeks' gestation PMA
3. Successful implementation of non-invasive support or ventilation (preferably bubble CPAP) within
        a) Part A: 90 minutes after birth
        b) Part B: 60 minutes after birth
4. Spontaneous breathing

5. Chest radiograph consistent with RDS (may be deferred if in the best medical interest of the subject)
6. Respiratory support:
   a) Part A: Within the first 20 hours after birth, requires an nCPAP of 5 to 7 cm H_2O with an FiO_2 of ≥0.25 (>0.21 for neonates 28 weeks PMA) to 0.4 that is clinically indicated for at least 30 minutes to maintain SpO_2 of 90% to 95%.
   b) Part B: Within the first 12 hours after birth, requires an nCPAP of 5 to 7 cm H_2O with an FiO_2 >0.21 to 0.4 that is clinically indicated for at least 20 minutes to maintain SpO_2 of 90% to 95%.

   Transient (<10 minutes) FiO_2 excursions outside this range do not reset the time requirement.

4.3 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 (PROM) > 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 already received)

11. Presence of air leak (pneumothorax, pneumomediastinum, pneumopericardium, subcutaneous emphysema, or definite evidence of pulmonary interstitial emphysema [PIE]) on the baseline chest radiograph

5 STUDY TREATMENT DOSING AND ADMINISTRATION

Preterm neonates who meet all of the inclusion criteria and none of the 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 one of the active treatment groups or to the control group. All subjects will receive standard neonatal care in the NICU. Subjects randomized to an active group will receive lucinactant for inhalation via the ADS in conjunction with nCPAP. Subjects randomized to the control group will receive nCPAP only. In order to maintain masking in Part A of the study, 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. In Part B of the study, control subjects will continue on nCPAP without sham treatment. All subjects, including controls, may receive repeat treatments if repeat dosing criteria are met (Part A: up to 2 repeat treatments; Part B: up to 4 repeat treatments). Subjects randomized to an active treatment group may be administered additional exposures of lucinactant for inhalation within 36 hours of randomization (Part A: up to 2 additional exposures; Part B: up to 4 additional exposures). Subjects in Part A randomized to control may receive an additional 1 or 2 sham treatments while receiving nCPAP; those in Part B randomized to control will continue on nCPAP.

To maintain masking in Part A, study treatment will occur behind a visual barrier; the PI, study staff (eg, site coordinator) (as applicable), and attending physician as appropriate will not be allowed to observe preparation of study materials, setup of the device, or to observe the subject during study treatment unless an emergent condition develops. The sponsor (as applicable) and the parents/legal guardian will also remain masked. Part B of the study will be open-label. (See also Section 5.6.)

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 Discovery at the earliest time point possible.

5.1 AEROSURF Delivery System

The ADS creates and delivers aerosolized surfactant (lucinactant for inhalation) via 2 components (Figure 5-1): the durable ACU (Section 5.1.1) and the disposable ADP (Section 5.1.2). The ADS is designed for bedside use and is mounted on a wheeled cart for easy transport.

Details for study drug preparation and ADS operation are provided in the AEROSURF Investigator's Brochure 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 a single 60 mL syringe and transferred into the provided ADP syringe, which is then loaded into the ACU. 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.

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.

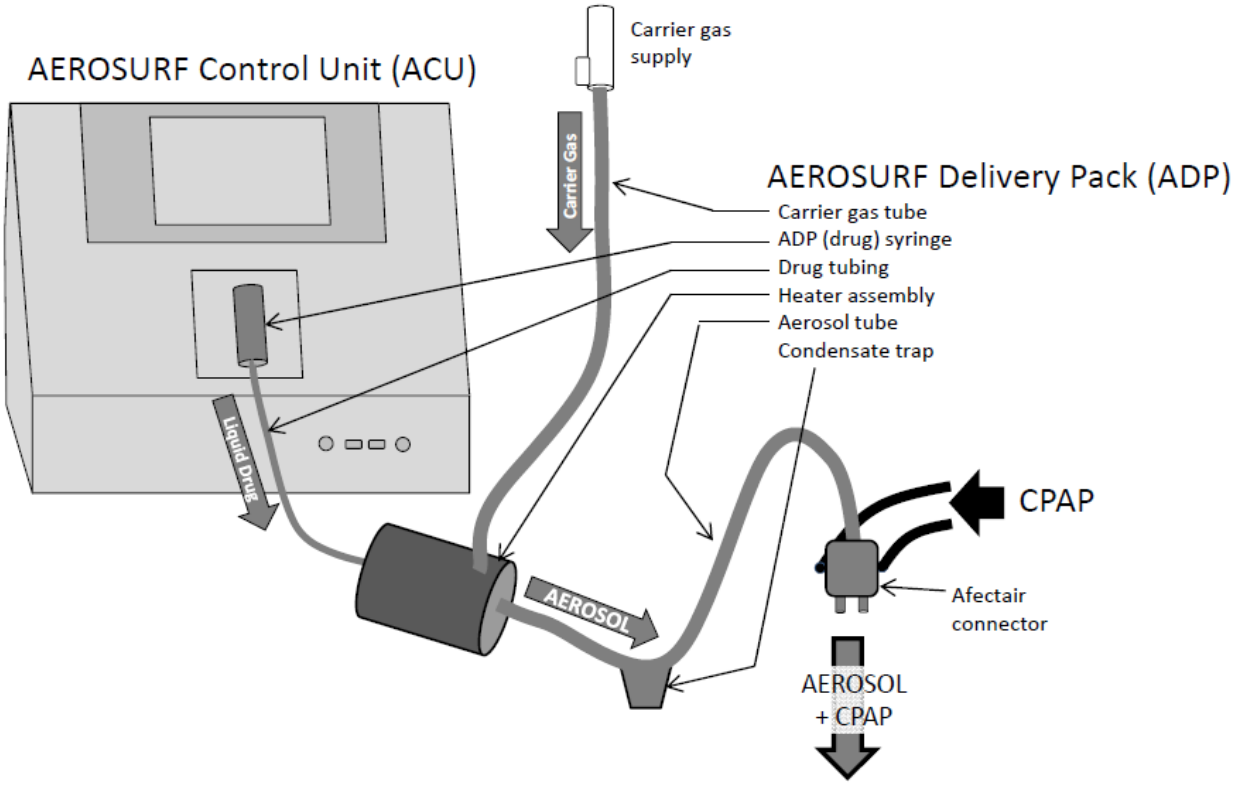

Figure 5-1. Schematic Diagram of the Aerosol Delivery System

The ADS aerosolizes lucinactant through heat and pressure created within the CAG located within the heater assembly. Together, the ADP and ACU produce, control and monitor the key elements necessary for the aerosolizing lucinactant.

5.1.1 AEROSURF Control Unit

The ACU contains a syringe pump mechanism and a temperature probe integrated with control electronics, which allows it to measure and control the heater to enable aerosol generation. The control electronics consist of embedded hardware and software with a touch screen interface that provides sequential instruction for ADS set-up and system operation, as well as safety interventions and control of the temperature of the heater. The syringe is contained within a chamber with a locking door, which prevents access to the syringe after aerosolization is started. A cart is provided for use with the ACU. Materials and dimensions for the ACU are consistent with equipment typically used in critical care environments.

5.1.2 AEROSURF Delivery Pack

The ADP is a single-use, disposable pack containing a 60-mL syringe, the carrier gas and the aerosol tube assemblies, and the heater assembly. The 60 mL syringe is filled with reconstituted lucinactant for inhalation, which pumped by the ACU through tubing to the heater assembly, which heats the lucinactant for inhalation and produces the aerosol. The carrier gas tube carries gas from an external source (usually a blend of air and oxygen) to the heater assembly, where it then drives the aerosol through the aerosol tube. Instructions for the proper set-up, connection, breakdown and return of ADP components are provided in the ADS Operator's Manual. One ADP will be required for each treatment, with an additional ADP required for each repeat dose.

Further information and instructions on ADP shipping and accountability are provided in the Study Manual.

5.2 Identity of Investigational Drug Product

The complete list of ingredients for the drug product is shown in Table 5-1.

5.2.1 Formulation of Study Drug

The drug product (lucinactant) is supplied as a sterile, white, liposomal powder consisting of a 21-amino acid hydrophobic synthetic peptide, (sinapultide, KL_4 peptide), the phospholipids dipalmitoylphosphatidylcholine (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.

Table 5-1. 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

5.2.2 Aerosol characteristics

The aerosol is generated at a formulation flow rate of approximately 1.2 mL/min. The mass mean 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. Approximately 65% of the aerosolized dose condenses within the delivery tubing, leaving approximately 35% available for inhalation by the subject at the connection to the nCPAP patient interface. A disposable fluid trap collects the aerosol that condenses within the delivery tubing. Calculations for the theoretical maximum inhaled dose are given in Section 2.2.3.2. The specification for the aerosol temperature at the patient interface is 25°C to 38°C.

5.2.3 Packaging and Labeling

Lucinactant is supplied in 30-mL glass vials packaged in cartons with foam inserts to reduce breakage.

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

5.3 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 Discovery 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 AEROSURF® Delivery Packs [ADPs]). Details on study supply accountability and storage are provided in Section 5.9 and in the ADS Operator's Manual.

5.3.1 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 also closely monitored for complications related to placement of the patient interface (see Section 9).

5.3.2 Precautions for Device Usage

Before using the ADS on study subjects, clinicians must have completed all required study training. All local and regional NICU requirements for the operation of an investigational NICU device must be followed.

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 must contact Discovery immediately for further instructions (Section 9.2.1). In such cases, the subject must be removed from the device, and 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.

5.4 Description of Treatment Groups

The study treatment, 'lucinactant for inhalation,' consists of the investigational drug lucinactant and the delivery system ADS. The ADS has two components, the ADP and the AEROSURF® Control Unit (ACU), described fully in Section 5.1. The rationale for the selected device and study treatments, including active and control, is discussed in Section 2.2.

5.4.1 Aerosol Delivery in the Active Treatment Groups

5.4.1.1 Study Part A

Study treatment is to begin within 2 hours after randomization. For subjects randomized to the active study treatment groups, the duration of treatment is 25 or 50 minutes (corresponding to 40 or 80 mg TPL/kg, respectively) in accordance with the subject's treatment group. Repeat doses (up to 2) at the same dosage/duration are to be given if repeat dosing criteria are met unless it is unsafe to do so in the judgment of the investigator (see Section 5.7). All study treatments are masked (see Section 5.6).

5.4.1.2 Study Part B

Study treatment is to begin within 2 hours after randomization; however, every effort should be made to begin study treatment as soon after randomization as possible (ideally, within 30 minutes). For subjects randomized to the active study treatment group, the duration of treatment is 50 minutes (corresponding to 80 mg TPL/kg). Repeat doses (up to 4) of 80 mg TPL/kg are to be given if repeat dosing criteria are met unless it is unsafe to do so in the judgment of the investigator (see Section 5.7). All study treatments are open-label.

5.4.2 Treatment in the Control Groups

As described in Section 2.2.2, no inert placebo exists. The appropriate control is to remain on nCPAP alone without study drug treatment, which is the control in Part B of the study. For Part A of the study, the optimal masked 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 along with an inactive syringe in a masked manner. Masking will occur as with active treatment (eg, behind a curtain). The ADS itself will be brought to the bedside but not used (since doing so would trigger alarms that would break masking). Control subjects in Part A of the study will be randomized to either a sham of 25 minutes or a sham of 50 minutes. The start time will be the time at which the sham setup is complete and the nCPAP circuit is interrupted; the stop time will be either 25 or 50 minutes later, depending upon the randomization. The subject will remain masked for the same duration as active subjects. At the end of the assigned sham treatment time, the subject will be switched to clean nCPAP equipment, as occurs at the end of active treatment. Masking equipment may then be removed.

As with active treatment, control/sham treatment in Part A of the study is to begin within 2 hours after randomization. Repeat control/sham treatments (up to 2) for the same duration as the initial treatment are to be given if repeat dosing criteria are met unless it is unsafe to do so in the judgment of the investigator (see Section 5.7). As described in Section 2.2.2, repeat treatment with control/sham in subjects who do not require intubation is ethical.

Control subjects in Part B of the study will receive sham treatment (subject will be placed on the study interface); the ADS does not need to be brought to the bedside. Control subjects in Part B will not receive repeat treatments.

5.5 Treatment Groups and Method of Treatment Group Assignment

Subjects will be assigned to receive either 40 or 80 mg/kg lucinactant for inhalation in conjunction with nCPAP or control (nCPAP only, with sham treatment of 25 or 50 minutes in Part A of the study) (Table 5-2).

Table 5-2 Study Assignments by Treatment Groups

Treatment Group	Study Assignment
Study Part A[a]	
40 mg/kg	Lucinactant for inhalation 40 mg TPL/kg (administered over 25 minutes) in conjunction with nCPAP (n = up to 80) Up to 2 repeat doses of lucinactant for inhalation 40 mg TPL/kg are to be given if repeat dosing criteria are met
80 mg/kg	Lucinactant for inhalation 80 mg TPL/kg (administered over 50 minutes) in conjunction with nCPAP (n = up to 80) Up to 2 repeat doses of lucinactant for inhalation 80 mg TPL/kg are to be given if repeat dosing criteria are met
Control	Continuous nCPAP with sham drug treatment (n = up to 80)
Study Part B	
80 mg/kg	Lucinactant for inhalation 80 mg TPL/kg (administered over 50 minutes) in conjunction with nCPAP (n = up to 40) Up to 4 repeat doses of lucinactant for inhalation 80 mg TPL/kg are to be given if repeat dosing criteria are met
Control	Continuous nCPAP (n = up to 40)

[a]Note: In Part A of the study, masking procedures for the initial dose will be followed for all repeat doses in all treatment groups

In Part A of the study, preterm neonates who successfully meet all eligibility criteria will be randomly assigned within their applicable stratum (28 completed weeks PMA or 29 to 32

completed weeks PMA) to one of the 3 treatment groups in a 1:1:1 ratio. In Part B of the study, preterm neonates who successfully meet all eligibility criteria will be randomly assigned within their applicable stratum (26, 27, and 28 completed weeks PMA) to one of the 2 treatment groups in a 1:1 ratio.

Subjects will be randomized using centralized allocation electronically (eg, interactive web response system [IWRS]). 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.

The randomization code list will be generated by Discovery Biometrics personnel. For Part A of the study, the code list will use a block size of 6 (40 mg TPL/kg ×2, 80 mg TPL/kg ×2, sham treatment of 25 minutes, sham treatment of 50 minutes), stratified by PMA. For Part B of the study, the code list will use a block size of 4 (80 mg TPL/kg ×2, sham treatment of 50 minutes ×2).

5.6 Study Masking

In order to minimize bias in subject assessments, study treatment masking (blinding) will be employed in Part A of the Study. Details of the masking procedure are provided in the 03-CL-1202 Overall Blinding Plan, Blinding Procedure, Blinding Maintenance and Assurance Plan, and Statistical Analysis Plan documents. The blinding plan is outlined as follows:

a. 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 assignment is required for patient management, then the blind may be broken. If this occurs, then Discovery must be notified as soon as possible (see Section 9.2.2).

b. Personnel making or influencing clinical decisions – especially regarding intubation or the level of respiratory support until a subject reaches 72 hours of life – 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 Discovery prior to site's participation in the study.

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 (for controls). At the conclusion of treatment, the dosing team will replace any visibly soiled nCPAP equipment, break down the dosing equipment, remove all residual active drug, remove the visual barriers, and transport the waste (obscured from view) for disposal and the ADS back to storage.

In order to facilitate administration of study treatment as early as possible in Part B of the study, study treatment will be open-label. As discussed in Section 1.3.2.2 and 2.2.3.5, it is likely that in neonates 26 to 28 weeks PMA study drug will need to be administered earlier and in higher dosages (or with more and earlier repeat doses) than has been done in Study 03-CL-1401 and in Part A of this study. Experience from Part A of this study to date has shown that set-up and breakdown of masking equipment has proven somewhat of a hindrance to early study treatment administration. Discovery has determined that the potential benefit of earlier study treatment administration outweighs the potential detriment of open-label administration compared to masked treatment.

5.7 Repeat Dosing

5.7.1 Study Part A

Up to 2 repeat doses will be administered to each subject, regardless of treatment group assignment, up to 36 hours following randomization. For each subject, repeat doses will consist of the same dosage/duration as the initial dose (including control/sham) and will occur if repeat dosing criteria are met, unless it is unsafe to do so in the judgment of the investigator. As

described in Section 2.2.2, repeat dosing with control/sham is ethical. Masking procedures used for the initial dose will be followed for repeat doses (see Section 5.6).

The repeat dosing criteria for Part A of the study are defined as follows:

a. Time: ≥2 hours from completion of the previous dose (up to 36 hours following randomization)

b. Respiratory support: Subject has a sustained (≥30 minutes) need for FiO_2 above the qualifying FiO_2 for study enrollment (≥0.25 for neonates 29-32 weeks PMA, >0.21 for neonates 28 weeks PMA) to maintain SpO_2 of 90% to 95%.

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

5.7.2 Study Part B

Up to 4 repeat doses will be administered to each subject randomized to active treatment, up to 36 hours following randomization. Repeat doses should be administered as soon as possible following the previous dose. Repeat doses will be administered if repeat dosing criteria are met, unless it is unsafe to do so in the judgment of the investigator. Repeat doses will be open-label.

The repeat dosing criteria for Part B of the study are defined as follows:

a. Time: ≥30 minutes from completion of the previous dose (up to 36 hours following randomization)

b. Respiratory support: Subject has a sustained (≥30 minutes) need for FiO_2 above the qualifying FiO_2 for study enrollment (>0.21) to maintain SpO_2 of 90% to 95%.

As with the initial dose, the randomization system will be used to receive the study drug kit assignments.

5.8 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 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, including certain error codes. If device failure or malfunction or error codes occur, Discovery personnel should be contacted immediately per Section 9.2.1).
2. Automatic treatment interruption due to an error condition (eg, syringe pressure out of range error). If error codes occur, Discovery personnel should be contacted immediately per Section 9.2.1).
3. An AE or ADE which places subject safety at risk occurs, eg, pulmonary hemorrhage.
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. An $FiO_2 \geq 0.70$ or a sustained increase from baseline by ≥ 0.30 to maintain SpO_2 90% to 95%

    b. A transcutaneous $PCO_2 > 70$ mm Hg or a progressive increase in PCO_2 from baseline to ≥ 20 mm Hg above baseline

    c. Recurring episodes of bradycardia (see Section 7.1.4)

    d. A sustained apneic event (see Section 7.1.4)

Subjects whose treatment is interrupted because of a device failure, malfunction, or error code may be administered a supplemental dose of lucinactant for inhalation in order to complete the interrupted dose with a total dosage as close to the initial target dosage as possible. 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 (see Section 10.2).

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

5.9 Clinical Study Supplies at the Clinical Study Site

5.9.1 Investigational Study Drug and ADPs

Lucinactant and ADPs will either be shipped directly to the investigational clinical study site pharmacies or to a designated location at the clinical study sites. A Clinical Supply Receipt Form will accompany the shipment. Study sites must verify each shipment via the Clinical Supply Receipt Form and study IWRS, and report study drug shipping temperatures to Discovery as outlined in the study manual.

5.9.2 Ancillary Supplies

Ancillary supplies (eg, nCPAP system, nasal prongs, and high pressure hoses) will be shipped directly to the investigational clinical study site NICU or to a designated location at the clinical study site. A Clinical Supply Receipt Form will accompany the shipment. Study sites must verify each shipment to Discovery via the Clinical Supply Receipt Form.

5.9.3 Dispensing

Study supplies (study drug/sham, ADP, and related study equipment) will be dispensed in accordance with the subject's randomized treatment group (Section 5.5). 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 ADP components (ie, ADP syringe and heater assembly) must be fully reconciled at the end of the study. The study clinical site monitor will provide oversight of these tasks and communicate any significant findings or indications of noncompliance to Discovery.

5.9.4 Storage of Lucinactant and AEROSURF Delivery System

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. Study sites must monitor and log storage temperatures. All temperature excursions should be reported to Discovery as outlined in the study manual (see also Section 9.2).

The ACU and ADPs 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.

5.10 Study Compliance

Study compliance 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 ACU, which will display a continual count of lucinactant exposure time throughout the aerosol delivery period. Duration of sham treatment will be based on randomization of subjects to a sham of 25 or 50 minutes. 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.

5.11 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, and related equipment) are inventoried and appropriately stored in accordance with study guidance documents (eg, study protocol, ACU Operator's Manual), and used only for study subjects, by study trained staff.

5.11.1 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 ADPs must be kept separate from unused supplies throughout the life of the study.
2. Designated study personnel will return all unused study drug vials and ADPs 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 clinical site monitor and recorded appropriately in the pharmacy log and drug and device accountability records.
4. Storage conditions, as described in the study manual, will be assessed and documented by the 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 in the inventory log and kept with the study site records throughout the study.

6. Designated study personnel (eg, pharmacists) will not supply study drug, ADPs, and ancillary supplies to any person other than designated study staff.
7. Study sites will not dispense the study supplies to any sites other than those listed on Form FDA 1572, Statement of Investigators.

6 DATA MONITORING COMMITTEE

The purpose of the 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. Safety and tolerability data will be assessed at pre-specified enrollment milestones. Data from the time all active subjects complete assessments and procedures through 72 hours of life will be reviewed. Enrollment will continue throughout each DMC review.

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

6.1 Safety Reviews

The DMC reviews will 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 3.3).

In addition to discrete reviews by the DMC as a whole, the DMC chairman will receive safety updates at least every other week. Following a thorough independent review of available study data, the DMC will provide timely recommendations to the Discovery 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 to be reviewed at each meeting.

6.2 Safety Enrollment Holds

Failed tolerability will be established based on analysis of AEs. In particular, AEs related to the administration of lucinactant for inhalation are of particular interest. To prevent undue risk to subjects, ongoing review of combined AEs and SAEs will occur. If more than 3 subjects experience the same SAE related to study treatment (not including nCPAP failure), or the sponsor determines a pattern of SAE occurrence, the DMC chair will determine if an ad hoc

meeting of the DMC will occur to review the safety information from the study. Any death within 24 hours of study treatment will be communicated to the DMC chair at the time of regulatory agency reporting, if applicable, or if not applicable, when information is available.

7 STUDY PROCEDURES AND GUIDELINES

A table of study procedures and assessments is presented in Appendix 2.

Before conducting any study-related activities, a signed written ICF and the Health Insurance Portability and Accountability Act (HIPAA) authorization (where applicable) must be signed and dated by the subject's parent or legally authorized guardian (Section 12.2).

7.1 Clinical Assessments

The clinical assessments described below must be appropriately documented in the study eCRF. In addition, any clinical findings comprising an AE must be documented as such in the eCRF (Section 9).

In addition to the clinical assessments outlined below, unmasked qualified medical personnel are to provide continual clinical assessment and monitoring during the active delivery of study treatment. If at any point during the delivery of study treatment a potential safety risk to the subject is identified, study treatment must be discontinued. Any significant clinical findings or observations must be documented and communicated to Discovery at the earliest time point possible (Section 9.2).

7.1.1 Vital Signs

Baseline vital signs (body temperature, respiratory rate, and heart rate) will be documented within 15 minutes (± 5 minutes) before randomization and at the following time points:

- Study Days 1-2, hours (± window) after randomization: 1±0.25, 3±0.25, 6±1, 12±1, 18±2, 24±2, 36±2, and 48±2
- Study Days 3-7: daily at 0800 hours (±2 hours)

In addition, vital signs (respiratory rate and heart rate only) will be documented during each study treatment (Section 7.1.10).

7.1.2 Body Weight

Birth weight will be documented in the study eCRF as part of the birth history.

7.1.3 Pulse Oximetry

Oxygen (O_2) saturations will be monitored by pulse oximetry (SpO_2) continuously from the time of randomization until completion of Study Day 7. SpO_2 will be documented in the study eCRF during each study treatment (Section 7.1.10). Additionally, SpO_2 serves as part of the definition of apnea and desaturation (Section 7.1.4).

7.1.4 Apnea, Bradycardia and Desaturation

In this study, the following definitions are used for apnea, bradycardia, and desaturation. Occurrences of each must be recorded as an AE.

Apnea is defined as a lack of inspiratory air movement sustained for ≥ 20 seconds and coincident with at least one of the following:

1. SpO_2 < 80% (not necessarily ≥20 seconds)
2. HR < 100 bpm (not necessarily ≥20 seconds)
3. Requirement for PPV administered manually or mechanically through any patient interface

Bradycardia is defined as a heart rate < 100 bpm sustained for ≥ 20 seconds.

Desaturation is defined as SpO_2 < 80% sustained for ≥ 20 seconds.

7.1.5 Monitoring of Carbon Dioxide Levels

Serum partial pressure of carbon dioxide (PCO_2) will be assessed for all subjects through the use of continuous transcutaneous monitoring. PCO_2 monitoring will be initiated following randomization at least 30 minutes before the start of initial dosing and must continue for 72 hours after randomization or until the subject is no longer receiving non-invasive support or ventilation, including nCPAP. 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.

Determinations of study conduct or classification, such as respiratory failure due to RDS (Section 3.2.1) or early stopping of study treatment (Section 5.8) may be made based on transcutaneous CO_2 values. If the transcutaneous monitor is not available or cannot be used,

subjects may be enrolled and measurements per institutional practice for method (eg, heel stick) and time points may be used.

PCO_2 will be documented in the study eCRF during each study treatment (see Section 7.1.10) and every 6 hours from randomization through 72 hours.

7.1.6 Physical Examination

A complete physical examination will be performed by the PI or designee. The designee may be a qualified member of the site-based study staff (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 must be documented as AEs in the eCRF and will be followed by a physician or other qualified staff until resolution.

7.1.7 Serum Electrolytes

Serum electrolytes (Na^+, Cl^-, K^+, and Total CO_2) will be measured 24 hours from the time of randomization (± 6 hours). Values obtained in the course of clinical management may be used in lieu of obtaining samples specifically for this study.

7.1.8 Chest Radiograph

A chest radiograph for the diagnosis of RDS and exclusion of air leak will be performed as part of the screening assessment. A radiograph obtained in the course of clinical management may be used in lieu of obtaining samples specifically for this study. Diagnostic chest radiograph may be deferred until after enrollment if in the judgment of the investigator the diagnosis of RDS is nearly certain and it is the best medical interest of the subject to receive study treatment as soon as possible. A blinded review of all radiographs may be performed by Discovery or designee.

A chest radiograph will also be required for study subjects who are intubated for any indication during the first 7 study days. All efforts must be made to obtain the chest radiograph prior to intubation, if the procedure does not delay or compromise the emergent care of the subject.

7.1.9 Defecation

The number of stools within the first 24 hours following randomization will be recorded in the study eCRF.

7.1.10 Clinical Assessments during Each Study Treatment Administration

During administration of each study treatment (active or sham/control, initial or repeat dosing), vital signs (heart rate and respiratory rate), FiO_2, SpO_2, and PCO_2 will be recorded at the start of study treatment and at 10, 20, 30, 40 and 50 minutes (±4 minutes) following the start of study treatment.

7.2 Medical Information

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, time relative to birth)
- 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 (Section 7.1.2), use of Sustained Inflation resuscitation technique
- Medical history from birth to randomization

7.3 Concomitant Medications

Concomitant 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 (see also Section 7.3.1).

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 NICU, 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.

7.3.1 Use of Additional Surfactant Replacement Therapies

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. Because conventional SRT requires endotracheal intubation (even if a tube other than an endotracheal tube is used), subjects receiving commercially available SRT will be

considered to have respiratory failure due to RDS (see Section 3.2.1). Such subjects remain in the study and are followed until study completion.

7.3.2 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 clear medical need is determined.

7.4 Demographics

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

7.5 Respiratory Support and Oxygen Delivery

7.5.1 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, etc.). The study nCPAP device is the specific nCPAP device and interface supplied for use with the ADS. Non-invasive support and non-invasive ventilation (NIV) refer to any device which generates a constant or variable positive pressure and uses a patient interface on the subject's face. nCPAP would therefore be a form of non-invasive support or ventilation with a constant airway pressure, while SiPAP, non-invasive positive pressure ventilation (NIPPV) and IPPB would be examples of NIV with variable pressures. MV refers to any device which generates a constant or variable positive pressure via an endotracheal tube or tracheostomy. Supplemental oxygen refers to 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 supplemental oxygen refers only to modes that deliver oxygen without pressure.

Study subjects must be maintained on study nCPAP from the time of randomization until at least 6 hours after they have completed delivery of each dose of study treatment as outlined in Section 7.5.3. The management of respiratory support (including nCPAP) and oxygen delivery is otherwise at the discretion of the study PI, keeping in mind that repeat doses of lucinactant for inhalation can be delivered only on study nCPAP.

The study definition of respiratory failure due to RDS (Section 3.2.1) is used for analysis purposes only; it is not intended to mandate or guide clinical decision making.

7.5.2 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 supplemental oxygen must be evaluated as a potential AE (Section 9) and reported in the study eCRF as such, if applicable.

7.5.3 Use of Nasal Continuous Positive Airway Pressure

Study treatment may be delivered only via the study nCPAP device and interface. Subjects must remain on study nCPAP for at least 6 hours following each study treatment; 12 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, unless the subject requires escalation in respiratory support to a different form of non-invasive ventilation or requires tracheal intubation. If a subject is switched from study nCPAP to an alternate form of non-invasive support within 12 hours of dosing, the reason will be documented in the eCRF. Settings on nCPAP are left to the investigator's judgment.

Changing to an alternate form of nCPAP or other form of non-invasive support or ventilation 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 non-invasive support or ventilation 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 re-dose, since in order 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 Discovery (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 (see Section 9).

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 7 cm H_2O is achieved. If a sustained nCPAP of >8 cm H_2O or FiO_2 ≥0.45 are necessary to maintain SpO_2 90 to 95% or if PCO_2 > 50 mm Hg, then other forms of non-invasive ventilation may be employed (see Section 7.5.4). If unsuccessful, the subject should be evaluated for clinical signs and symptoms consistent with respiratory failure due to RDS (Section 3.2.1).

7.5.4 Use of Non-Invasive Support before and after Enrollment

In subjects eligible for this study, non-invasive support or ventilation must be implemented within 90 minutes of birth; however, modes of support other than study nCPAP are acceptable. In the delivery room, intermittent positive pressure breaths may be administered manually or mechanically through a noninvasive patient interface (eg, mask or nasal prongs) for no longer than 10 minutes after birth (eg, NeoPuff). Following delivery, any mode of non-invasive ventilation or patient interface may be used to support respirations as clinically indicated, including nasal cannula; high-flow nasal cannula (eg, VapoTherm); nCPAP generated by flow (eg, bubble CPAP or RAM cannula) or mechanical ventilator and using any interface (eg, RAM cannula, nasal prongs, face mask, etc); bi-level positive airway pressure (eg, SiPAP, BiPAP); neutrally-adjusted ventilatory assistance (NAVA); non-invasive positive-pressure ventilation (NIPPV); etc.

Subjects are eligible for screening if any form of non-invasive support or ventilation is instituted within the required time period after birth (90 minutes for Part A of the study; 60 minutes for Part B) and the investigator feels it is safe to switch the subject to study nCPAP. After informed consent is obtained, subjects may be switched to study nCPAP/interface for screening. If the subject meets the inclusion criterion for respiratory support (Inclusion Criterion #6) and meets all

other inclusion/exclusion criteria, that subject may be enrolled. For Part A of the study, the respiratory support criterion requires that within the first 20 hours after birth the subject is stable for ≥30 minutes on nCPAP of 5-7 cm H_2O with FiO_2 0.25 (>0.21 for neonates 28 weeks PMA) to 0.4 to maintain SpO_2 90%-95%. For Part B of the study, within the first 12 hours after birth the subject must be stable for ≥20 minutes on nCPAP of 5-7 cm H_2O with FiO_2 >0.21 to 0.4 to maintain SpO_2 90%-95%.

Particularly for the 26 to 28 week PMA neonates in Part B of the study, support as early as possible with NIV and transition to study nCPAP is emphasized. Ideally, subjects will be placed on NIV or study nCPAP within 15 to 30 minutes of birth, switched to study nCPAP shortly thereafter if not already on it, and will be randomized and receive study treatment within 1-2 hours of birth. Such early treatment would likely require informed consent to be obtained prenatally.

Following dosing, subjects must be maintained on study nCPAP for at least 6 hours; 12 hours is strongly recommended, and ideally the subject will remain on study nCPAP until 36 hours following randomization (Section 7.5.3). After at least 6 hours, other forms of non-invasive support or ventilation may be employed, particularly if a subject requires increased respiratory support but does not require intubation and SRT. Clinical judgment should be used to guide ventilatory management. If nCPAP has escalated to 7 cm H_2O and subjects require additional support, non-invasive ventilation may be an option rather than increasing nCPAP further. Subjects requiring increased respiratory support should be considered for redosing if they are within the appropriate time frame and clinical conditions (Section 5.7).

7.5.5 Documentation of Respiratory Support Parameters

7.5.5.1 Documentation during the Primary and Extended Observation Periods

From the time of randomization until completion of Study Day 7, respiratory support parameters must be evaluated and documented in the study eCRF:

- The mode of respiratory support (including supplemental oxygen) and important parameters for that mode are documented at 0800 and 2000 daily. If the subject is on nCPAP, parameters are documented additionally at 1 and 3 hours following randomization, then every 6 hours until 48 hours following randomization.
- FiO_2 is documented every 6 hours from randomization through 72 hours along with transcutaneous PCO_2 (Section 7.1.5)

- Vital signs, FiO_2, SpO_2, and PCO_2 are documented during each study treatment (Section 7.1.10)
- Date and time are documented for each intubation and change of ventilatory support mode

7.5.5.2 Documentation during Final Observation Period

From Study Day 8 until the subject completes or withdraws from the study, the date and time of each intubation, change of ventilatory support mode (including supplemental oxygen), and important parameters for that mode must be evaluated and documented in the study eCRF.

7.5.5.3 Documentation during Longer-Term Follow-up Phase

During the longer-term follow-up phase, the start date/time and duration of each ventilatory support mode (including supplemental oxygen), and important parameters for that mode must be evaluated and documented in the study eCRF at 6 and 12 months corrected age (via telephone or report).

7.6 Assessment Parameters for Technical Performance of the Device

The following parameters will be captured in the eCRF in a blinded manner:

- Any issues associated with device tubing (eg, ventilator/CPAP tubing detachments, aerosol tube detachments, proximal pressure port obstruction, aerosol tube condensate obstruction).
- Approximate volume (in milliliters) of liquid in all the traps (at the completion of study drug administration)
- Aerosol or study drug leakage before the subject interface (eg, disconnect of the inspiratory circuitry).
- Occurrence of alarm signals before, during, or after dosing that may indicate a device malfunction.
- Any automatic system shutdowns.
- Loss of inspiratory flow to the neonate or inability to maintain nCPAP.
- ADS temperature alerts (high or low).

8 EVALUATIONS BY OBSERVATION PERIOD

All of the assessments performed for each subject from screening until the time the subject completes the study (36 weeks PMA) or withdraws (Section 10.2) are presented below. A table of study procedures and assessments is presented in Appendix 2.

8.1 Screening Period

The following information will be obtained for each subject before study enrollment:

- A signed ICF
- Inclusion and exclusion criteria (Sections 4.2 and 4.3)
- Demographics (Section 7.4)
- Maternal history (Section 7.2)
- Birth history and birth weight (Section 7.2)
- Medical History (Section 7.2)
- Initial full physical examination findings (Section 7.1.6)
- Chest radiograph (Section 7.1.8)
- Respiratory support and O_2 delivery (date and time of initial nCPAP or other type of non-invasive ventilation)

8.2 Primary Phase

8.2.1 Primary Observation Period

The following will be documented for each randomized subject during the Primary Observation Period of the study (within first 72 hours of life):

1. Date and time (T_0) of randomization and assignment to study treatment group (Section 5.5)
2. The date and time of the initiation and completion of each study drug or sham (control) treatment (Section 5)
3. Technical performance of the device (Section 7.6)
4. The use of pacifiers and/or chin strap during dosing (Section 5.3.1)
5. The use of an oro- or nasogastric tube
6. Vital signs (Sections 7.1.1 and 7.1.10)

7. SpO_2 (Sections 7.1.3 and 7.1.10)
8. Transcutaneous PCO_2 values (Section 7.1.5 and 7.1.10)
9. Assessment and documentation of respiratory support and supplemental oxygen (Section 7.5.5.1 and 7.1.10)
10. Serum electrolytes (Section 7.1.7)
11. Defecation (initial 24 hours following randomization) (Section 7.1.9)
12. Chest radiograph, as applicable (Section 7.1.8)
13. Incidence of all AEs, including ADEs, peri-dosing events, and complications related to placement of bi-nasal prongs (Section 9)
14. Survival (date, time, and cause of death if applicable)
15. Concomitant medications (Section 7.3)

8.2.2 Extended Observation Period

The following assessments are to be performed during the Extended Observation Period of the study (> 72 hours to ≤ 7 days after date of randomization). Daily measurements are to be obtained as close to 0800 as possible.

1. Chest radiograph, as applicable (Section 7.1.8)
2. Assessment and documentation of respiratory support and supplemental oxygen (Section 7.5.5.1)
3. The use of an oro- or nasogastric tube
4. Vital signs (Section 7.1.1)
5. SpO_2 (Section 7.1.3)
6. Incidence of AEs (Section 9)
7. Survival (date, time, and cause of death if applicable)
8. Concomitant medications (Section 7.3)

8.2.3 Final Observation Period (From Day 8 to 36 Weeks Postmenstrual Age/Final Observation [or NICU Discharge, Death, or Hospital Transfer])

The Final Observation Period from Day 8 to 36 weeks PMA/Final Observation, or NICU discharge, death, or hospital transfer (whichever occurs first), will include the following:

1. Abbreviated physical examination (including changes from baseline examination) (Section 7.1.6) (final observation only)

2. Assessment and documentation of respiratory support and supplemental oxygen (Section 7.5.5.1)
3. Incidence of AEs (Section 9)
4. Survival (date, time, and cause of death if applicable)
5. Concomitant medications (Section 7.3)
6. Incidence of BPD at 36 weeks PMA (see definition in Appendix 1)
7. Occurrence or presence of complications of prematurity (Section 9) and their treatments:
8. Date and time of transfer or discharge from the current hospital (if applicable)

8.3 Longer-Term Follow-Up Phase Through 1-Year Corrected Age

The following assessments are to be performed during the Longer-Term Follow-Up Phase from the final observation through 1-year corrected age.

At 6 months corrected age (±2 weeks), the following will be assessed:

1. Number of hospitalizations
2. Time on respiratory support (Section 7.5.5.3)
3. Concomitant medication: use of any bronchodilator or steroid

At 1-Year corrected age (± 4 weeks), the following will be assessed:

1. Number of hospitalizations
2. Time on respiratory support (Section 7.5.5.3)
3. Abbreviated physical examination
4. Abbreviated neurologic assessment
5. Concomitant medication: use of any bronchodilator or steroid

9 ADVERSE EVENT REPORTING

Information regarding the occurrence of AEs will be assessed from the time of randomization until completion of Final Study Observation. Incidence of ADEs will be assessed from the time of randomization until completion of the primary observation period.

For purposes of this study, the following will be considered AEs of special interest if they occur within the primary observation period:

1. Peri-dosing events, defined as the following AEs with an onset time ≤ 2 hours from the time of initiating study treatment:

    - Apnea (Section 7.1.4)
    - Bradycardia (Section 7.1.4)
    - Desaturation (Section 7.1.4)
    - Gagging/regurgitation
    - Pallor

2. Apnea (Section 7.1.4), after the peri-dosing period

3. Bradycardia (Section 7.1.4), after the peri-dosing period

4. Desaturation (Section 7.1.4), after the peri-dosing period

5. 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)

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
- Pulmonary interstitial emphysema [PIE]
- Pneumomediastinum
- Pneumopericardium
- Subcutaneous emphysema

Complications of prematurity include the following, but are not considered AEs of special interest:

- Intraventricular hemorrhage [IVH]
- Periventricular leukomalacia [PVL]
- Pulmonary hemorrhage
- Apnea
- Necrotizing enterocolitis [NEC]
- Patent ductus arteriosus [PDA]
- Acquired sepsis
- Retinopathy of prematurity [ROP]
- BPD

All AEs must be followed by the PI until resolution or for at least 30 days post-study if the subject is stable.

Documentation of AEs in the eCRF must include the following parameters; (1) duration (time of onset and resolution), (2) severity or grade, (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), version 18.1 or above.

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 related to the use of the investigational device. ADEs are treated the same as all other AEs. For serious ADEs, see unanticipated adverse device effects (UADE) in Section 9.1.5.

9.1.1 Causal Relationship of Adverse Events

The relationship of an AE to a study drug is assessed by the PI 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.
- 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

9.1.2 Severity Grade Levels of Adverse Events

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

- Mild: Symptoms causing no or minimal interference with usual social and functional activities
- Moderate: Symptoms causing greater than minimal interference with usual social and functional activities
- Severe: Symptoms causing inability to perform usual social and functional activities

9.1.3 Adverse Event Procedures

All AEs 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 Discovery).

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

A SAE is any untoward medical occurrence that, at any dose, 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-trained designee becomes aware of an SAE, Discovery must be notified as soon as possible (and no later than 24 hours after the event has occurred) via telephone or fax, regardless of the relationship (or lack thereof) of the SAE to study participation.

SAEs can be reported to the Discovery SAE reporting line, by country (see Section 9.2).

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. This should be emailed to the local clinical site monitor or faxed (Section 9.2.2).

In accordance with Discovery'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/REB 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, Discovery must be notified immediately through the following procedures (see also Section 9.2):

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

9.2 Discovery Contact Information

The names, telephone, and fax numbers of the individuals who should be contacted regarding trial-related questions and safety are listed below.

9.2.1 Trial-Related Questions

For trial-related questions, including drug- or device-related issues, please call your clinical site monitor.

9.2.2 Medical Monitoring

FOR MEDICAL QUESTIONS, PLEASE CONTACT THE MEDICAL MONITOR:

Steven G. Simonson, MD (Medical Officer)
Office: (215) 488-9474
Mobile: (267) 454-4931
email: SSimonson@DiscoveryLabs.com

Paul M. Shore, MD MS (Medical Monitor)
Office: (215) 488-9465
Mobile: (267) 663-3204
email: PShore@DiscoveryLabs.com

or,

Robert Segal, MD, FACP (Safety Monitor)
Office: (215) 488-9450
Mobile: (267) 237-7576
email: RSegal@DiscoveryLabs.com

IN LATIN AMERICA, CONTACT:

Carlos G. Guardia, MD
Office: +1 717 300 1415
Mobile: +56 9 4203 9028
Email: CGuardia@Windtreetx.com

FOR SERIOUS ADVERSE EVENTS OR UNANTICIPATED ADVERSE DEVICE EFFECTS, PLEASE CONTACT DISCOVERY:

North America:

24 Hour Safety Hotline: +1 800 201 8725

Safety Hotline Fax : +1 888 488 9697

Latin America:

24 Hour Safety Hotline Voice: +55 11 4504 4801

Safety Hotline Fax: +55 11 3958 0983

European Union:

24 Hour Safety Hotline: +44 1223 374 240

Safety Hotline Fax: +44 1223 374 102

FOR ADDITIONAL ASSISTANCE, PLEASE CONTACT THE CLINICAL SITE MONITOR OR:

Judy Varga (Associate Director, Clinical Sciences, Discovery)
Mobile: (267) 614-2364
email: JVarga@Windtreetx.com

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 5.8) 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 guardian) at any time without prejudice to further care.

If a subject is discharged or transferred from the NICU 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, every effort must be made to contact the subject's legally authorized guardian to determine the status of the subject. 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 6).

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.
- Discovery, 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/REB, 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 violation occurs when the PI fails 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 7.3)
- Failure to comply with ICH GCP guidelines

Discovery will determine if a protocol violation will result in withdrawal of a subject.

A protocol deviation occurs when the PI fails to adhere to any protocol requirement that is not a protocol violation. Protocol deviations include collection of information outside a collection window or failure to collect non-critical information.

When a protocol violation or deviation occurs, it will be discussed 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 59th WMA General Assembly, Seoul, Korea, October 2008.

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 also 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/REB for each study site for approval to conduct the study. Before the initiation of the study at each study site, Discovery must be provided with a copy of the IRB/IEC/REB 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/REB 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/REB and written verification that the modification was submitted and subsequently approved should be obtained. A site must receive approval from Discovery on any ICF modification before submission to the IRB/IEC/REB for approval and subsequent implementation at the study site. Protocol modifications (ie, amendments) may only be enacted by Discovery.

The IRB/IEC/REB 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/REB)
2. Any new study information that may adversely affect subject safety or study conduct
3. Annual study updates or IRB/IEC/REB 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 Discovery. Completed site-based ICFs must be provided to Discovery or designee for approval before submission to the IRB/IEC/REB. The ICF generated by the PI must be acceptable to Discovery and be approved by the IRB/IEC/REB. The PI will send an IRB/IEC/REB approved copy of the ICF to Discovery 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/REB-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. If allowed by the IRB/IEC/REB, informed consent may be obtained prenatally.

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 Discovery, before participating in the study. In addition, clinical investigators will be required to consult with Discovery 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:

1. Initiating agency audits of the data derived from the clinical investigator in question
2. Requesting that the sponsor submit further data analyses (eg, to evaluate the effect of the clinical investigator's data on overall study outcome)
3. Requesting that the applicant conduct additional independent studies to confirm the results of the questioned study
4. 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 240 subjects (up to 80 per treatment group) will be enrolled into the study in Part A, and up to 80 subjects (up to 40 per treatment group) will be enrolled into the study in Part B.

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 Statistical and Analytical Plans

The statistical analysis of both the primary and secondary objectives will be based on all enrolled preterm neonates. For the efficacy analysis, all randomized subjects (intent-to-treat [ITT]) and subjects with no major protocol deviations (per-protocol) will be evaluated, based upon the treatment group to which they were randomized. 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 Parts A and B of the study for all subjects combined by treatment group and by gestational age (for Part A only).

All continuous variables (eg, weight, body temperature, transcutaneous PCO_2) will be summarized using number (n), mean, standard deviation (SD), median, 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 or death due to RDS within 72 hours of life) is defined in Section 3.2.1. The incidence of respiratory failure or death due to RDS will be compared between each active treatment and control using the Cochran-Mantel-Haenszel test, controlling for pooled sites.

Key secondary endpoints include the time to respiratory failure or death due to RDS, compared between each active treatment and control using the log-rank test. BPD, all-cause mortality, and common complications of prematurity (primarily air leak) will be compared using the Cochran-Mantel Haenszel test. Physiologic parameters (ie, FiO_2, transcutaneous PCO_2) will be compared using ANOVA with treatment and pooled study site 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, but will not be compared statistically. Physical examination and medical history will similarly be summarized. Vital signs (ie, body temperature, respiration rate, pulse) will be summarized as for continuous variables; vital signs will not be compared statistically.

13.2 Interim Analyses

The data monitoring committee (DMC) will conduct 2 preplanned interim analyses during Part A of the study: 1) after approximately 25% of subjects have been enrolled and 2) after 66% of subjects have been enrolled. The DMC will be provided full safety listings for review after 50% of subjects have been enrolled in Part B, but will not conduct a formal interim analysis. Study enrollment may be suspended if safety concerns are identified during any review (see Section 6).

In addition, a review of the treatment effect may be conducted by an independent statistical analysis center (ISAC) after approximately 50% of the subjects have been enrolled in Part A. The ISAC will assess the time and incidence of respiratory failure due to RDS by treatment group. These results will be used to determine if adjustments to the doses being studied should be considered. The *p*-values may or may not be adjusted, as appropriate.

13.3 Sample Size and Randomization

A total of up to 240 study subjects (up to 80 per treatment group) will be enrolled in Part A of the study, and a total of up to 80 study subjects (up to 40 per treatment group) in Part B. For Part A, the sample sizes were calculated separately for incidence of respiratory failure or death due to RDS, time to respiratory failure or death due to RDS, and a reduction in FiO_2. The sample size will have 90% power to detect the difference between treatment groups using a log-rank test for equality of time to event curves, assuming a constant hazard ratio of 0.500, within the first 72 hours of life. In addition, the sample size is sufficient to, separately, detect a reduction of 50% in the incidence of respiratory failure due to RDS within the first 72 hours of life, or a reduction

in FiO_2 of 4 percentage points (eg, 30% to 26%) within the first 24 hours following treatment (nQuery Advisor®, version 7.0).

In addition, the sample size is sufficient to provide a stable estimate of the size of the treatment effect (treatment delta). The efficacy estimate will be used to calculate the sample size for future studies.

For Part B, formal sample size calculations have not been conducted. A total of 40 subjects per group is sufficient to provide a stable estimate of the size of the treatment effect.

Efficacy and safety will be assessed for each part separately and for all subjects combined.

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/REB reviews, as well as access and review of source data by Discovery 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 Discovery. 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; however, data may be entered directly into the eCRF in fields which require free-text entries as directed by the sponsor. Subjects will not be identified by name in the study database or on any study documents to be collected by Discovery (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 Discovery'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 Discovery 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 Discovery 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. Discovery must be notified in writing of the name and address of the new custodian.

14.7 Monitoring

Discovery 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, Discovery 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/REB review and approval of the study before study initiation at his/her clinical site, and ensure timely updates to the IRB/IEC/REB as mandated by local and national regulatory requirements, and to

ensure timely communications to Discovery of all IRB/IEC/REB 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) as soon as possible, and in no case later than 24 hours after the event, to the medical monitor or designee at Discovery.
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 ADP (including heater assembly [ADP] and syringe [ADPS] serial numbers) 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 Discovery. Protocol amendments will not be implemented without prior written IRB/IEC/REB 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/REB 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 has completed the study. Continuation of this study beyond this time must be agreed upon by both the PI and Discovery and may be implemented without amendment to the protocol.

15.3 Study Report

Discovery 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 Discovery 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 3 and, in Canada, Appendix 4), the PI agrees to:

1. Conduct the study in accordance with the protocol and only make changes after notifying Discovery 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/REB 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 Discovery 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 Discovery, designee, or Regulatory Agency.
7. Ensure the study site is fully aligned with their local IRB/IEC/REB.
8. Ensure the local IRB/IEC/REB 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/REB and Discovery 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/REB 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.

16 REFERENCES

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17 APPENDICES

Appendix 1 Protocol Definitions

Definitions	
Aerosol, study	Output of ADS device (eg, aerosolized lucinactant)
Aerosol, time	Duration a subject is exposed to aerosolized lucinactant
Air leak, pulmonary	Chest radiographic evidence of air leak (pneumothorax, pulmonary interstitial emphysema, 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) at 36 weeks PMA	The need for oxygen supplementation (FiO_2 > 0.21) at 36 weeks PMA.
Corrected age	Age of the subject from the date the subject reaches 40 weeks gestation.
Desaturation	SpO_2 < 80% sustained for ≥ 20 seconds
Final Observation	The final study observation is to occur at 36 weeks PMA or at the time of NICU discharge or hospital transfer (whichever occurs first). If the neonate dies, the final observation will be considered the last study observation before death.
Gestational age	Gestational age of the subject based on the mother's last menstrual period based on best obstetrical estimate or ultrasound.
Non-invasive support	Any respiratory support device which generates a constant positive pressure and uses a patient interface on the subject's face.
Non-invasive ventilation (NIV)	Any respiratory support device which generates a 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.

Peri-dosing event	One of the following AEs with an onset time ≤2 hours from the time of initiating study treatment: • Apnea • Bradycardia • Desaturation • Gagging/regurgitation • Pallor
Period, extended observational	The study timeframe occurring >72 hours from randomization until ≤ Day 7
Period, final observational	The study timeframe occurring > day 7 to ≤ 36 weeks PMA
Period, primary observational	The study timeframe occurring ≤72 hours from randomization
Physical exam	Includes the following organ systems: cardiac, respiratory, abdomen, genitalia and perineum, skin, extremities, head, neck and mouth, and neurological.
Study treatment	Receipt of either active or sham/placebo dosing, either initially or as a repeat. Masking procedures for the initial dose will be followed for repeat doses.
Supplemental oxygen	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 supplemental oxygen refers only to modes that deliver oxygen without pressure.

Appendix 2 Protocol Event Schedule

Measurement/Procedure	Primary Phase Through 36 Weeks PMA				Longer-Term Follow-Up Phase Through 1-Year Corrected Age
	Screening	Primary Observation (Days 1 to 3)	Extended Observation (Days 4 to 7)	Final Observation (Day 8 to 36w PMA/ Final Observation)	
Informed Consent/HIPAA (or applicable local privacy regulations)	X				
Inclusion/Exclusion Criteria	X				
Demographics	X				
Maternal History	X				
Birth History and Birth Weight	X				
Medical History	X				
Physical Examination[1]	X			X	
Chest Radiograph[2]	X	X	X		
Respiratory support and O_2 delivery	X	X	X	X	X
Randomization		X			
Study Treatment (drug or sham) Administration		X[3]			
Technical Performance of Device		X			
Use of pacifier and/or chin strap during dosing		X			
Use of oro- or nasogastric tube		X	X		
Vital Signs[3]		X	X		
SpO_2		X	X		
Transcutaneous PCO_2		X			
Serum Electrolytes		X			
Defecation		X			
Adverse Events		X	X	X	
Adverse Device Effects		X			

Measurement/Procedure	Primary Phase Through 36 Weeks PMA				Longer-Term Follow-Up Phase Through 1-Year Corrected Age
	Screening	Primary Observation (Days 1 to 3)	Extended Observation (Days 4 to 7)	Final Observation (Day 8 to 36w PMA/ Final Observation)	
Survival		X	X	X	
Concomitant Medication		X	X	X	X
Incidence of BPD				X	
Complications of Prematurity				X	
Hospitalizations					X
Abbreviated physical and neurological exam					X

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

[1] Physical exam is performed at screening and at the final observation at the end of the Final Observation Period only

[2] A chest radiograph will be performed as part of the screening assessment. An additional chest radiograph is required prior to intubation is required if such a procedure does not delay or compromise the emergent care of the subject.

[3] Body temperature, respiratory rate and heart rate are documented on a schedule based on the date and time of randomization. Respiratory rate and heart rate are additionally documented every 10 minutes during study treatment administration.

Appendix 3 Investigator Agreement Form

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

Study Number: 03-CL-1202

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/Research Ethics Board and Discovery Laboratories, Inc. (Discovery) and will fulfill all responsibilities for submitting pertinent information to the IRB/IEC/REB responsible for the study.

I further agree that authorized representatives of Discovery, 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 Discovery 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 Discovery 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: _____

Appendix 4 Investigator Agreement Form for Canada

Investigator's Agreement in Accordance with Subsection 81(k) of the Medical Devices Regulations Canadian Sites

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

Study Number: 03-CL-1202

Device Name: Aerosurf™ Delivery System

I, as the qualified investigator for the above referenced clinical trial, undertake, as outlined in Subsection 81(k) of the *Medical Devices Regulations,* to:

i. conduct the investigational testing in accordance with the protocol,
ii. inform a patient who is to be diagnosed or treated with the device of the risks and benefits associated with its use and obtain the written consent of the patient,
iii. not use the device or permit it to be used for any purpose other than the investigational testing specified in the protocol,
iv. not permit the device to be used by any person other than myself, except under my direction, and
v. in the event of an incident that is related to a failure of the device or a deterioration in its effectiveness, or any inadequacy in its labelling or in its directions for use and has led to the death or a serious deterioration in the state of health of a patient, user or other person, or could do so were it to recur, report the incident and the circumstances surrounding it to Discovery Laboratories, Inc. as soon as possible (and no later than 24 hours after the event has occurred) and to the Canadian Medical Devices Bureau within 72 hours after it comes to my attention.

Completed forms should be emailed to: mdpr-dimm@hc-sc.gc.ca or faxed to: 613-954-0941 or mailed to:

Canada Vigilance - Medical Device Problem Reporting Program
Marketed Health Products Directorate
Health Canada
Address Locator 0701E
200 Tunney's Pasture Driveway
Ottawa (Ontario) K1A 0K9

Qualified Investigator and Site Information	
Printed Name	Title
Name of Site	
Address	
Signature	Date