A MULTICENTER, RANDOMIZED, OPEN-LABEL, CONTROLLED TRIAL TO ASSESS THE SAFETY AND TOLERABILITY OF LUCINACTANT FOR INHALATION IN PRETERM NEONATES 26 TO 28 WEEKS PMA

Protocol No.:	03-CL-1401
Study Phase:	2a
Investigational Product:	Aerosurf® (lucinactant for inhalation)
IND Number:	119438

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A Multicenter, Randomized, Open-Label, Controlled Trial to Assess the Safety and Tolerability of Lucinactant for Inhalation in Preterm Neonates 26 to 28 Weeks PMA

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AEROSURF PROTOCOL SUMMARY

Protocol Number	03-CL-1401
Title:	A Multicenter, Randomized, Open-Label, Controlled Trial to Assess the Safety and Tolerability of Lucinactant for Inhalation in Preterm Neonates 26 to 28 Weeks PMA
Phase:	2a
US IND Number:	119438
Sponsor:	Discovery Laboratories, Inc. (Discovery), Warrington, PA, USA
Committees:	Steering Committee, Safety Review Committee (SRC)
Study Drug and Device	Lucinactant for inhalation (an investigational, drug-device combination product) at 30 mg total phospholipids (TPL)/ml delivered by the Aerosurf® delivery system (ADS) utilizing a capillary-based aerosol generator (CAG).
Active Ingredients:	A 21-amino acid hydrophobic synthetic peptide (sinapultide, KL_4 peptide), combined with the phospholipids dipalmitoylphosphatidyl-choline (DPPC) and palmitoyloleoyl-phosphatidylglycerol, sodium salt (POPG, Na), and the fatty acid palmitic acid (PA).
Rationale:	Preterm neonates are often surfactant deficient and receive surfactant replacement therapy (SRT) to treat respiratory distress syndrome (RDS). Currently, the preterm infant has SRT instilled directly into the lung through an endotracheal tube while receiving positive pressure mechanical ventilation. However, data from studies in animal models of RDS suggest that endotracheal intubation and positive pressure mechanical ventilation administered by an endotracheal tube may be injurious to the preterm lung. Therefore, clinical practice has evolved over the past decade toward avoidance of the use of endotracheal intubation, thereby foregoing SRT, and instead utilizes non-invasive means to provide ventilatory support, including nasal continuous positive airway pressure (nCPAP), to support preterm newborns with mild to moderate RDS. However, large multicenter trials have

demonstrated respiratory deterioration in one-third to one-half of preterm neonates receiving nCPAP, who then progress to requiring endotracheal intubation, mechanical ventilation, and in many cases SRT. Meta-analyses of clinical surfactant studies indicate that SRT is most effective when administered early in the course of RDS, and the therapeutic benefit of SRT can diminish substantially when administered later in the course of the disease. Therefore, the inability to administer SRT without endotracheal intubation results in suboptimal timing for SRT in preterm infants who are initially supported with nCPAP who then deteriorate and require endotracheal intubation and SRT to treat RDS.

The inability to administer SRT without the need for endotracheal intubation represents an unmet medical need. Aerosolized surfactant delivery potentially addresses this unmet medical need by providing a means to deliver SRT to preterm neonates with RDS supported with nCPAP, thereby providing SRT early in the disease course while avoiding the need for endotracheal intubation.

The lucinactant for inhalation clinical program is intended to study preterm infants 26 to 28 completed weeks post-menstrual age (PMA). Currently, preterm infants 29 to 34 completed weeks PMA are being studied in Protocol 03-CL-1201. To date, lucinactant for inhalation has been shown to be generally safe and well-tolerated. Since there have been no safety signals of concern in later preterm infants, this study (03-CL-1401) will evaluate earlier preterm infants (26 to 28 completed weeks PMA) for safety and tolerability.

Primary Objective: The primary objective of this study is to evaluate the safety and tolerability of lucinactant for inhalation, administered as an aerosolized dose in 4 escalating doses to a preterm, neonatal population 26 to 28 completed weeks PMA receiving nCPAP for RDS compared with neonates receiving nCPAP alone. Safety and tolerability will be evaluated using the same measures and assessments that have been used in Protocol 03-CL-1201, which has shown lucinactant for inhalation to be generally safe and well-tolerated in infants 29 to 34 completed weeks PMA.

Secondary Objective: The secondary objectives of this study are to determine the maximum tolerated dose of lucinactant as determined by the safety evaluations

obtained within each dosing group, and to assess the feasibility of evaluating physiological pulmonary function parameters as a measure of improvement in clinical status in preterm neonates 26 to 28 completed weeks PMA who are receiving nCPAP for RDS, compared with neonates receiving nCPAP alone.

Study Design:

This multicenter, randomized, controlled, dose-escalation study, will evaluate the safety and tolerability of lucinactant for inhalation in conjunction with nCPAP in comparison with nCPAP alone in preterm infants 26 to 28 completed weeks PMA with RDS. For this study, lucinactant for inhalation refers to the active investigational agent, lyophilized lucinactant, in combination with the investigational delivery device, ADS.

Preterm neonates between 26 and 28 completed weeks PMA who are within the first 20 hours after birth and who had successful implementation of controlled nCPAP within 90 minutes of birth will be considered to be potential subjects. Before study enrollment, legal guardians will provide a 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. Inclusion criteria to be met within the first 20 hours after birth includes a required nCPAP of 5 to 6 cm H_2O to maintain SpO_2 of 88% to 95% with a fraction of inspired oxygen (FiO_2) within a range of 0.25 to 0.50 for at least 30 minutes. As soon as study eligibility has been confirmed and the informed consent is signed, subjects will be randomized to either an active arm or a control arm. Subjects randomized to an active arm will receive 1 dose of lucinactant for inhalation within 2 hours of randomization; subjects must continue to meet entry criteria at the time of initiation of study therapy. Active study therapy will be administered through the investigational ADS device over 30, 45, 60, or 90 minutes in conjunction with nCPAP support.

Subjects may be eligible to receive a repeat dose between 2 and 24 hours after the initial dose if subjects meet repeat dosing criteria, as

described in the "Treatment Groups" section. Subjects randomized to a control arm will be continued on nCPAP alone.

A safety assessment will be performed by an independent SRC after each group has been enrolled. All subjects on the active arm will receive the same drug concentration of lucinactant for inhalation at the same rate. The dose will vary by the volume of the nominal dose of lucinactant (30 mg TPL/ml) aerosolized and introduced into the nCPAP circuit, given over a predetermined time for each dose. The lucinactant for inhalation delivery will be facilitated by the investigational ADS device in conjunction with a commercially available nCPAP generator and patient interface.

Dose assignments will be un-blinded, as the primary objective of this study is safety and tolerability. Preliminary efficacy endpoints will be assessed as an exploratory objective.

All enrolled subjects will receive study treatment in a neonatal intensive care unit (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. Infants 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, mechanical ventilation, and surfactant administration will be readily available to all study subjects if clinically indicated in accordance with the high level standard of care customary in the NICU.

Neonates will be followed through the primary phase evaluations through 36 weeks PMA, NICU discharge, hospital transfer, or death, whichever occurs first.

Study Population:

This study will be comprised of preterm neonates 26 to 28 completed weeks PMA who are receiving care in a NICU and are eligible to receive nCPAP support for RDS.

The study population will consist of 4 escalating dose groups with an allowed repeat dose if repeat dose criteria are met. Repeat dosing is to ensure subjects with a demonstrated need will receive additional treatment, as is done with bolus dosing.

Study Sample Size:	It is anticipated that approximately 64 subjects will be enrolled. Approximately 32 subjects will be randomized to the active arm (drug/device combination) and approximately 32 subjects will be randomized to the control arm (nCPAP alone). The sample size is based on the number of subjects necessary to evaluate safety and tolerability of lucinactant for inhalation. Sample size calculations to demonstrate a clinical effect will not be performed as efficacy is an exploratory objective. Subjects that do not complete the administered dose of lucinactant for inhalation, or withdraw from the study will not be replaced, unless required by the SRC in order to adequately assess safety in the dose group.
Number of Sites:	Up to approximately 25 clinical sites in the US; sites outside the US may also be used.
Study Duration:	Overall study enrollment will be completed in approximately 7 months, with the last subject completing their last visit approximately 9 months from the time of the first subject enrolled. Subject participation will be from ≤ 20 hours following birth until 36 weeks PMA or discharge, whichever comes first.
Method of Administration:	Subjects randomized to the active study arm 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 device, ADS (using the CAG), and introduced into the nCPAP circuit. Those randomized to the control arm will continue to receive nCPAP alone. The exposure time will be based on the nominal dose, defined as the volume of lucinactant aerosolized by the ADS. Exposure, defined as the emitted dose, is the amount of lucinactant that is delivered at the connection to the patient interface by the ADS at a constant rate of flow. Because of losses that occur as the lucinactant aerosol travels from the ADS to the patient interface, the emitted dose is approximately 35% of the nominal dose. The theoretical inhaled dose, the fraction of the aerosolized lucinactant that the infant is exposed to that is likely to be inhaled, is estimated by product of the aerosol concentration, the minute ventilation of the infant, and the administration time of the aerosol.

Dosing Groups:

Dosing Group I	Active Arm (n = 8): 50 mg TPL/kg administered over 30 minutes in conjunction with nCPAP 1 Repeat dose of 50 mg TPL/kg administered over 30 minutes is allowed if repeat dosing criteria are met. Control Arm (n = 8): Continuous nCPAP
Dosing Group II	Active Arm (n = 8): 75 mg TPL/kg administered over 45 minutes in conjunction with nCPAP 1 Repeat dose of 75 mg TPL/kg administered over 45 minutes is allowed if repeat dosing criteria are met. Control Arm (n = 8): Continuous nCPAP
Dosing Group III	Active Arm (n = 8): 100 mg TPL/kg administered over 60 minutes in conjunction with nCPAP 1 Repeat dose of 100 mg TPL/kg administered over 60 minutes is allowed if repeat dosing criteria are met. Control Arm (n = 8): Continuous nCPAP
Dosing Group IV	Active Arm (n = 8): 150 mg TPL/kg administered over 90 minutes in conjunction with nCPAP 1 Repeat dose of 150 mg TPL/kg administered over 90 minutes is allowed if repeat dosing criteria are met. Control Arm (n = 8): Continuous nCPAP

Each dosing group will complete study dosing and all active subjects will complete 72 hour safety assessments and procedures before the SRC review. The SRC will review all available safety data (to include study-related adverse events [AEs], including adverse device effects [ADEs], serious adverse events [SAEs], and additional safety endpoints). Enrollment will continue in the next dosing group without pause from the previous dosing group; however, if the SRC identifies safety concerns that would preclude dosing, enrollment will stop until these safety concerns are addressed and the SRC recommends resuming enrollment.

Repeat dosing will be allowed in each dosing group. Subjects meeting the repeat dosing criterion will receive an additional treatment of the same dose. Repeat dosing will be allowed between 2 hours and 24 hours after completion of the initial dose if subjects require a sustained need for supplemental oxygen at or above the qualifying FiO_2 level for study entry (ie, 0.25) for at least 30 minutes to maintain SpO_2 of 88% to 95%.

Subjects will be followed for safety evaluations (including, but not limited to, AEs and concomitant medications) until the subject is

36 weeks PMA or is discharged. A final visit will occur at 36 weeks PMA or at the time of discharge or withdrawal (whichever occurs first) for all subjects.

Inclusion Criteria:

1. Signed ICF from legally authorized representative;
2. Gestational age 26 to 28 completed weeks PMA;
3. Successful implementation of controlled nCPAP within 90 minutes after birth;
4. Spontaneous breathing;
5. Chest radiograph consistent with RDS;
6. Within the first 20 hours after birth, requires an nCPAP of 5 to 6 cm H_2O to maintain SpO_2 of 88% to 95% with an FiO_2 of 0.25 to 0.50 that is clinically indicated for at least 30 minutes. Transient (<10 minutes) FiO_2 excursions below 0.25 or above 0.50 do not reset the 30 minute requirement.

Exclusion Criteria:

1. Heart rate that cannot be stabilized above 100 beats per minutes within 5 minutes of birth;
2. Recurrent episodes of apnea occurring after the initial newborn resuscitation period (ie, 10 minutes after birth) requiring intermittent positive pressure breaths using inflating pressures above the set CPAP pressure administered manually or mechanically through any patient interface;
3. A 5 minute Apgar score < 5;
4. Major congenital malformation(s) and cranial/facial abnormalities that preclude nCPAP, diagnosed antenatally or immediately after birth;
5. Other diseases or conditions potentially interfering with cardiopulmonary function (eg, hydrops fetalis or congenital infection such as TORCH);
6. Known or suspected chromosomal abnormality or syndrome;
7. Premature rupture of membranes (PROM) > 2 weeks;
8. Evidence of hemodynamic instability requiring vasopressors or steroids for hemodynamic support and/or presumed clinical sepsis;
9. Need for endotracheal intubation and/or mechanical ventilation;
10. Has been administered any the following:
    a) Another investigational agent or investigational medical

device,
b) Administration of any other surfactant agent,
c) Steroid treatment (exposure before birth is acceptable).

Note: All subjects must continue to meet entry criteria at the time of initiation of study therapy.

Concomitant Medications:

All concomitant medications administered to the subject from birth until 36 weeks PMA, NICU discharge, hospital transfer, or death (whichever comes 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 lucinactant for inhalation administration or control, 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 (as per the protocol). Postnatal steroids are not permitted unless clear medical need is determined.

Safety and Tolerability Measures:

Primary and Secondary Safety and Tolerability Measures:

- Primary Observation Period (Day 1 and 2):
  1. Survival
  2. Use of respiratory support and supplemental oxygen
  3. Incidences leading to early discontinuation of aerosolized lucinactant administration
  4. Incidence of worsening respiratory status
  5. Incidence of air leak
  6. AEs, including ADEs (specifically including peri-dosing events and nasal excoriations)
  7. Complications of prematurity
  8. Concomitant medication
  9. Physical exam findings
  10. Tolerability of lucinactant for inhalation
  11. Assessments of the following:
      a) Vital signs
      b) Oxygen saturations (SpO_2)

c) Partial pressure of carbon dioxide (PCO_2) values
d) FiO_2 values
e) Serum electrolyte measurements
f) Body weight
g) Gastric liquid volume
h) Defecation

12. Chest radiography prior to non-emergent intubation, or in cases of worsening respiratory status, if such a procedure does not delay or compromise the emergent care of the subject

- Extended Observation Period (Day 3 until Day 7):
  1. Survival
  2. Incidences leading to withdrawal from study
  3. Incidence of worsening respiratory status
  4. AEs, including ADEs
  5. Complications of prematurity
  6. Concomitant medication
  7. Assessment of the following:
     - Vital signs
     - O_2 saturation values
     - FiO_2 values through 72 hours
     - PCO2 values through 72 hours
  8. Chest radiography prior to non-emergent intubation, or in cases of worsening respiratory status, if such a procedure does not delay or compromise the emergent care of the subject.
  9. Use of respiratory support and supplemental oxygen
- Final Observation Period (Day 8 to 36 Weeks PMA or discharge):
  1. Survival
  2. Incidences leading to withdrawal from study
  3. Incidence of worsening respiratory distress
  4. AEs, including ADEs
  5. Physical exam findings

6. Concomitant medications
7. Use of respiratory support and supplemental oxygen
8. Complications of prematurity

Efficacy Measures (Exploratory)

1. Technical performance of the ADS

   The efficacy of the device delivery of lucinactant for inhalation will be characterized indirectly through the subject's response to treatment and solicited feedback from the principal investigators (PIs) and relevant site-based study staff.
2. Incidence of bronchopulmonary dysplasia (BPD)
3. Rate of survival without BPD at 36 weeks PMA (as applicable)
4. Worsening respiratory status either during or after exposure to lucinactant for inhalation
   A. A subject will be categorized as having worsening respiratory status if they meet at least 1 of the following criteria: (1) need for additional surfactant therapy following exposure to lucinactant for inhalation; (2) a sustained (> 30 minutes) $FiO_2 > 0.50$ to maintain an $SpO_2 > 90\%$; (3) a $PCO_2 > 65$ mm Hg on ≥ 2 consecutive observations; (4) persistent, arterial pH < 7.20 (if blood gas values are available and obtained for non-study related clinical assessment); (5) any sustained apneic event, defined as ≥ 20 seconds and at least one of the following: (a) HR < 100 bpm, (b) desaturation (oxygen saturation < 80%), (c) requirement for intermittent positive pressure (IPP) breaths using inflating pressures above the set CPAP pressure administered manually or mechanically through any patient interface; (6) intubation for any reason (except for elective surgical procedures); (7) nCPAP > 7 cm H_2O; (8) initiation of IPP breaths using inflating pressures above the set CPAP pressure administered manually or mechanically through any patient interface; (9) death while on study; or (10) the study PI determines the subject to have worsening respiratory status based on their best clinical judgment.
   B. Early worsening: worsening respiratory status occurring ≤ 72 hours after birth
   C. Late worsening: worsening respiratory status occurring > 72

hours and ≤ 7 days after birth

All subjects meeting the criteria of worsening respiratory status will continue to be followed for safety evaluations until 36 weeks PMA or discharge.

5. Physiological Parameters

   FiO_2 and PCO_2 will be evaluated as potential efficacy parameters.

Stopping Rules: The discontinuation of lucinactant for inhalation and the criteria for enrollment hold are the same as those used in Protocol 03-CL-1201. The administration of lucinactant for inhalation may be discontinued at any time in accordance with the clinical judgment of the PI or the wishes of the subject's legal guardian. In accordance with local institutional practices, SRT must be made available to subjects demonstrating a clinical need following exposure to lucinactant for inhalation.

Reasons for discontinuation from study drug administration include the following:

- Device failure or malfunction, including error codes or treatment interruptions;
- Pulmonary hemorrhage or other AE/ADE;
- In the PI's best medical judgment, initiating or continuing the subject's exposure to lucinactant for inhalation is not in the best interest of the subject's safety, such as hemodynamic instability.
- Signs of acute respiratory deterioration as evidenced by an increased respiratory rate or an observed increase in respiratory effort (work of breathing) plus at least one of the following:
  a) An FiO_2 ≥ 0.70 or a sustained (≥ 10 minutes) increase from baseline by ≥ 0.30 to maintain adequate oxyhemoglobin saturation (SpO_2 ≥ 88%),
  b) A PCO_2 > 70 mm Hg or a progressive increase from baseline to ≥ 20 mm Hg above baseline and confirmed with a blood gas,
  c) Recurring episodes of bradycardia defined as a heart rate < 100 bpm for ≥ 20 seconds,
  d) A sustained apneic event, defined as apnea for at least 20

seconds in duration and meeting at least one of the following: (1) HR < 100 bpm, (2) desaturation (oxygen saturation < 80%), (3) requirement for IPP breaths using inflating pressures above the set CPAP pressure administered manually or mechanically through any patient interface.

Enrollment hold criteria:

The study will be placed on enrollment hold until further evaluation by the SRC if one of the following criteria are met:

- If > 2 subjects per dosing group experience a SAE related to lucinactant for inhalation administration
- If ≥ 1 subject dies during first 12 hours following and related to lucinactant for inhalation administration

Statistical Analysis: The statistical analysis of both the primary and secondary safety and tolerability objectives will be based on all randomized preterm neonates in the study. In addition, data from all evaluable preterm neonates will be analyzed for efficacy signals as an exploratory endpoint. No hypothesis testing or statistical comparisons will be performed.

Interim Analyses: All available safety endpoint data captured from randomization to completion of 72 hours for active subjects, and all available safety endpoint data for control subjects, will be evaluated by the SRC. As this is an open-label study with no hypothesis testing, no adjustments for *p*-values are required or employed for the interim analyses.

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

Abbreviation	Description
ABG	Arterial blood gas
ACU	Aerosurf Control Unit
AE	Adverse event
ADE	Adverse device effect
ADS	Aerosurf Delivery System
ADP	Aerosurf Delivery Packet
BPD	Bronchopulmonary dysplasia
CAG	Capillary aerosol generator
CFR	Code of Federal Regulations
CPAP/nCPAP	Continuous positive airway pressure/nasal CPAP
CRF/eCRF	Case report form/electronic CRF
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
NOEL	No observed adverse effect level
PA	Palmitic acid
PCO_2	Partial pressure of carbon dioxide
PaO_2	Partial pressure of oxygen dissolved in arterial blood
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 tolerability of a sequential, escalating dose of lucinactant for inhalation (a non-invasive, investigational drug-device combination product) administered in preterm neonates 26 weeks to 28 completed weeks (28 weeks 6 days) post-menstrual age (PMA) with respiratory distress syndrome (RDS) treated with nasal continuous positive airway pressure (nCPAP), in comparison with nCPAP alone.

Non-invasive surfactant delivery potentially addresses an unmet medical need by providing a means to deliver surfactant to preterm neonates with RDS treated with nCPAP, thereby providing surfactant therapy early in the disease course while avoiding the complications associated with endotracheal intubation for surfactant delivery.

This phase 2a study is designed to assess the safety and tolerability of a novel surfactant replacement therapy (SRT), lucinactant for inhalation, administered at select doses in preterm infants 26 to 28 completed weeks PMA. A similar study, Protocol 03-CL-1201, in preterm neonates 29 to 34 completed weeks PMA, was conducted first to establish that lucinactant for inhalation is generally safety and well tolerated. Similar to this study (03-CL-1401), Protocol 03-CL-1201 evaluated lucinactant for inhalation in a dose-escalation manner up to 75 mg total phospholipids (TPL)/kg, with a currently ongoing study extension in that population up to 150 mg TPL/kg. Findings from these two studies (03-CL-1201 and 03-CL-1401) will contribute to the development and design of future investigations of this novel drug/device combination product.

All study procedures and assessments are to be conducted in accordance with local and regional regulatory requirements, institutional review board (IRB)/independent ethics committee (IEC) requirements, International Conference on Harmonisation Good Clinical Practices (ICH GCP) Guidelines, and local institutional practices. In addition, the study procedures and assessments are designed to mimic those of Protocol 03-CL-1201.

Definitions of study terms are provided in Appendix 1.

1.1 Treatment of Neonatal Respiratory Distress Syndrome

Surfactant treatment has reduced mortality and morbidity in newborns with RDS. Intratracheal[(1)] instillation of exogenous surfactant is a standard treatment for the treatment of RDS, and the benefits of surfactant treatment, specifically early surfactant treatment, are well established[(2)].

However, instillation of surfactant into the lung requires endotracheal intubation, an invasive procedure that has potential deleterious effects.

1.1.1 Continuous Positive Airway Pressure in Neonatal Respiratory Distress Syndrome

Efforts by neonatologists to avoid endotracheal intubation to reduce the volutrauma and barotrauma associated with airway inflation and deflation have focused on the use of nCPAP, reserving intubation and surfactant administration for the most severely ill neonates.

The use of nCPAP in preterm neonates with RDS has become widely accepted[3] and national guidelines (American Association for Respiratory Care)[4] exist for treatment of respiratory distress in preterm newborns. These guidelines outline several patient interface devices that can be used to deliver continuous airway pressure such as nasal masks, short bi-nasal prongs, and nasopharyngeal tubes. It has been demonstrated that nCPAP is effective in increasing functional residual capacity by stabilizing and improving alveolar function[5] and in dilating the larynx[6]. Devices that generate and deliver nCPAP, including patient interfaces such as nasal prongs, are specifically designed, manufactured, and commercially available for use in neonates.

While the use of nCPAP in preterm infants is common, studies of nCPAP alone, including a meta-analysis of prophylactic nCPAP for preventing morbidity and mortality in very preterm neonates, have not shown a clear benefit of this approach[7]. A large, multicenter, randomized clinical study (N = 610) was performed to compare the effects of nCPAP alone versus intermittent mechanical ventilation (IMV) for very preterm neonates at birth. This study showed that in the nCPAP group, the need for surfactant therapy was half of that compared to subjects in the intubation group, and death or oxygen treatment at day 28 after birth was less frequent ($p = 0.006$). However, there were no differences in survival or supplemental oxygen therapy at 36 weeks, overall mortality, days of respiratory support, oxygen treatment, hospital stay, or other secondary outcomes. Of note, a higher rate of pneumothorax in the nCPAP group compared to the intubation group (9% versus 3%) was observed, and over 50% of infants in the nCPAP group required endotracheal intubation[8]. Other studies comparing nCPAP to endotracheal intubation and surfactant administration have also demonstrated a relatively high rate of endotracheal intubation in the group receiving nCPAP.

1.2 Development of Aerosolized Device for Lucinactant Delivery

Discovery Laboratories, Inc. (Discovery) has developed a capillary aerosol generator (CAG) device to aerosolize lucinactant (lucinactant for inhalation). Pre-clinical studies using the CAG

technology in spontaneously breathing preterm lambs receiving aerosolized lucinactant have demonstrated significant improvements in lung mechanics and gas exchange compared with lambs receiving CPAP alone. In addition, pilot clinical studies using aerosolized lucinactant in neonates with RDS, as well as in adults with asthma and cystic fibrosis, have demonstrated that aerosolized lucinactant appears to be generally safe and well-tolerated.

1.2.1 Non-invasive Surfactant Delivery

Data from a large neonatal database support the assumption that prophylactic use of aerosolized surfactant and nCPAP may reduce the need for intubation by 36% in neonates with a birth weight of 1001 to 1500 grams [3].

Because aerosolized surfactant is preferentially delivered to the ventilated parts of the lungs, it is essential to provide appropriate ventilatory support during aerosol delivery. Distribution of aerosol in the lungs has been limited by the technical constraints of currently available aerosol generators and system configurations. Compared with the endotracheal instillation surfactant administration route, efforts to aerosolize surfactants in clinical models have been largely unsuccessful because of the highly inefficient and limited dose delivery compared with the bolus administration route of currently available aerosol generators [9,10]. However, the CAG technology may allow for administration of aerosolized lucinactant to be deposited in the lungs of preterm neonates in potentially sufficient quantities to affect a therapeutic response analogous to that of endotracheal instillation surfactant administration. An investigational device, Aerosurf Delivery System (ADS) utilizing the CAG has been developed and provides a high-density surfactant aerosol output (20 µl/sec), with an appropriate particle size (2 to 3 microns mass median aerodynamic diameter [MMAD]). The ADS will be used in 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 commercially available nebulizers (KL4-CPAP-01, KL4-ASTH-01). These studies demonstrated that delivery of lucinactant as an aerosol is technically feasible and that it is generally safe and well-tolerated in both adult patients and preterm neonates. In addition, one study (03-CL-1201) is being conducted with aerosolized lucinactant administered using the ADS. The preliminary results from 03-CL-1201 demonstrate that delivery of lucinactant as an aerosol using the CAG technology is feasible and that lucinactant for inhalation appears to be generally safe and well-tolerated in infants 29 to 34 weeks PMA.

1.3.1 Study KL4-CPAP-01

KL4-CPAP-01 was a phase 2, multicenter pilot study in preterm neonates investigating the feasibility of prophylactic, aerosolized lucinactant administered in conjunction with nCPAP. The study was designed to establish the feasibility of delivering prophylactic aerosolization of lucinactant to preterm neonates at risk for RDS[11]. A total of 17 neonates were enrolled and evaluated through 28 days of age.

The drug-device combination study consisted of a conditioning system and in-line Aeroneb® Pro Nebulizer System, which aerosolized lucinactant that was diluted from 30 mg/ml TPL to 20 mg/ml TPL. Treatment delivery was administered in conjunction with a nCPAP system and short bi-nasal prongs. The predetermined, theoretical maximum aerosolized, inhaled dose was 0.4 mg TPL per minute. Therefore, over a 3-hour period, the total, potential maximum lucinactant inhaled dose under breathing conditions of 6.4 ml tidal volume and 54 breaths per minute was 72 mg TPL. The predetermined Aeroneb Pro Nebulizer System output rate based on bench testing was approximately 4 μL/second. Thus, the total drug dispensed volume was 43 ml over 3 hours. With 3 re-treatments, the total potential drug exposure was up to 288 mg and 172 ml over a 48-hour period which, when calculated based on the average weight of the subjects entered into the trial would translate to approximately 192 mg/kg and 115 ml/kg, respectively. Since the majority of infants received only a single dose of study drug, most infants received approximately 72 mg TPL of aerosolized lucinactant in a volume of 43 ml over the 3 hour treatment.

The study demonstrated it is feasible to deliver aerosolized lucinactant in conjunction with nCPAP and that the treatment was generally safe and well tolerated by preterm neonates.

1.3.2 Study KL4-ASTH-01

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 safe and well tolerated.

1.3.3 Study 03-CL-1201

03-CL-1201 is a phase 2a multicenter, randomized, open-label, controlled study assessing the safety and tolerability of aerosolized lucinactant delivered using the ADS in preterm infants 29 to 34 completed weeks PMA. This is a dose-escalation study has recently completed enrollment in Dosing Group IV (100 mg TPL/kg and control [nCPAP only]). As the extension phase of this study is ongoing, full results are not yet available; however, preliminary results from Dosing Groups I, II, III, and IV indicate tolerability with the combination product. Reviews of the data conducted by the Safety Review Committee (SRC) for Dosing Groups I, II, III, and IV indicate that lucinactant delivered via the ADS is safe and well tolerated and the SRC has recommended continuing to the final extension dosing group (Dosing Group V) (see Section 2.2.3.2). The dosing regimen for the extension phase of the study by protocol amendment includes two additional dosing groups: Dosing Group IV, 100 mg TPL/kg with a possible repeat dose and Dosing Group V, 150 mg TPL/kg with a possible repeat dose.

This current protocol (03-CL-1401) has been designed to use the same procedures and assessments as Study 03-CL-1201, but in a younger patient population.

1.4 Regulatory Agency Meetings

Two meetings (1 pre-investigational new drug [pre-IND] meeting and 1 type C meeting) were held with the US Food and Drug Administration (FDA) on April 5, 2006, and July 18, 2007 to discuss the proposed development program for lucinactant for inhalation. During these meetings, Discovery agreed to perform 2 toxicology studies using lucinactant and the CAG technology in 2 species, with 1 of the species being non-rodent. These studies were completed and yielded a no-observed-adverse-effect–level (NOAEL) at the maximum feasible dose, as described in Section 2.2.3.1.

Discovery also acknowledged that the study population for the clinical program would be preterm neonates at risk for or with RDS. Discovery further acknowledged that the lucinactant aerosolized by the CAG technology would be tested for safety in a dose escalation study, and that testing would first be conducted in neonates at approximately 30 weeks PMA before testing in neonates at lower gestational ages. This dose-escalation study (Protocol 03-CL-1201) has recently completed enrollment through Dosing Groups I, II and III (25, 50 and 75 mg TPL/kg, respectively), and preliminary results indicate that lucinactant for inhalation is generally safe and tolerated. As was originally planned, with the conclusion of enrollment in Dosing Group III and

approval by the SRC to proceed to study a younger preterm population (ie, 26 to 28 completed weeks PMA), enrollment in Protocol 03-CL-1401 will begin.

2 STUDY DESIGN AND RATIONALE

This study will investigate the safety and tolerability of up to 4 escalating exposures with a potential repeat dose of lucinactant for inhalation. The study design will include up to 4 dosing groups consisting of preterm neonates 26 to 28 completed weeks PMA with RDS who are candidates for nCPAP and SRT.

2.1 Study Design

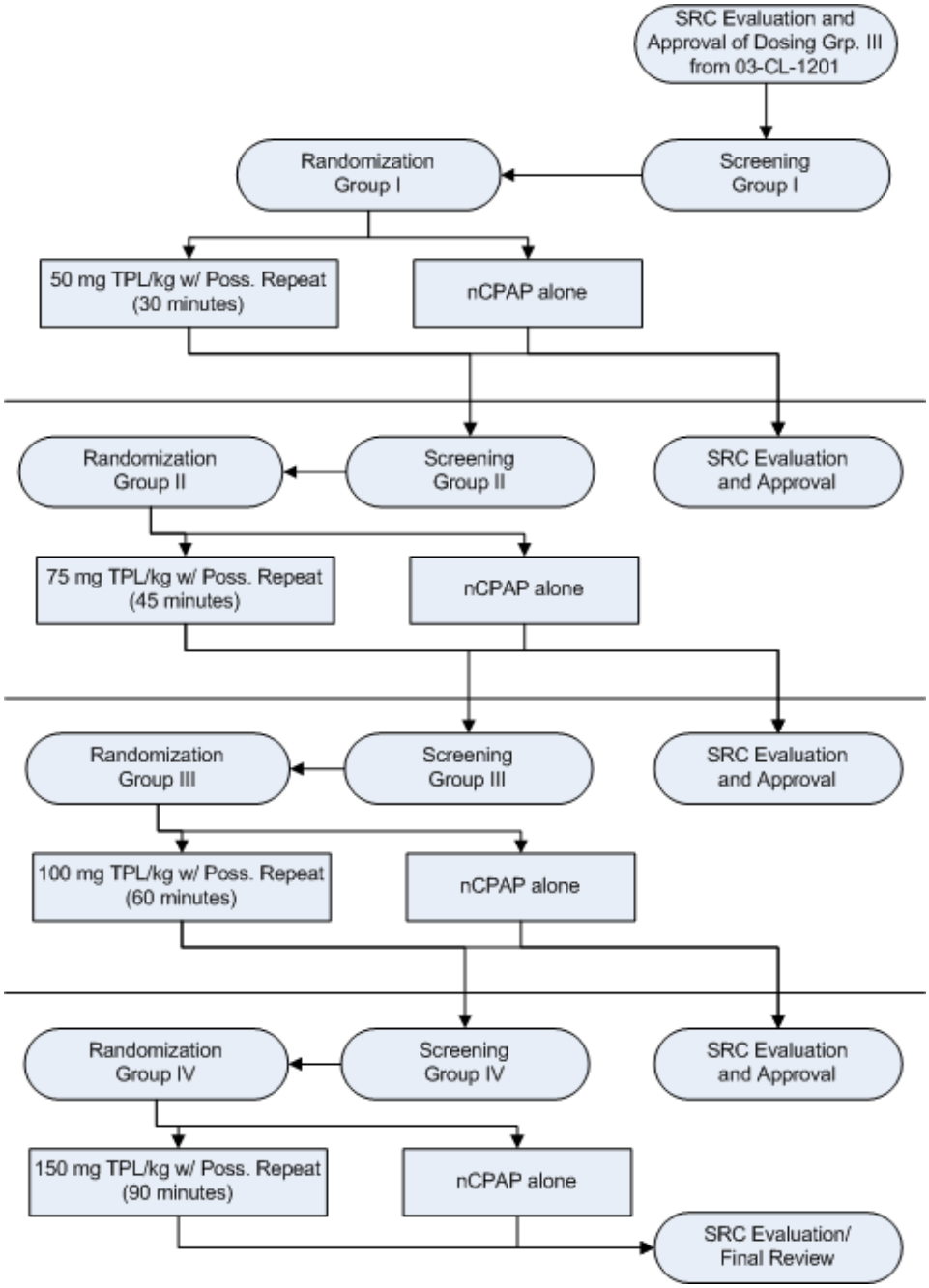
This study is a multicenter, randomized, open-label, controlled study to evaluate the safety and tolerability of a novel drug-device combination investigational product (lucinactant for inhalation) administered in conjunction with nCPAP, in preterm neonates with RDS who are under the care and observation of a neonatal intensive care unit (NICU). The study will explore escalating exposures of lucinactant for inhalation in a sequential manner through 4 unique dosing groups. All subjects randomized to the active study arm will receive the same concentration of study drug to provide the same total dose exposure. Subjects randomized to the control arm will receive nCPAP alone. Dosing groups are outlined in Section 5.2.2.

The lucinactant for inhalation delivery will be facilitated by the investigational ADS device in conjunction with a commercially-available nCPAP generator and patient interface. Details on the drug delivery device are outlined in Section 5.3.

Eligible neonates will be randomized within 20 hours after birth. Aerosolization of lucinactant will be initiated within 2 hours after randomization.

The study is designed to sequentially increase dose exposure. After each sequential dose, an independent SRC will review all adverse events and specified safety parameters (Section 6) (Figure 2.1-1).

Figure 2.1-1 Schematic of Study Design for 03-CL-1401



2.2 Dose and Device Description

In this study, approximately 32 subjects will be randomized to an active arm and will receive aerosolized lucinactant through the ADS (utilizing CAG technology) in conjunction with nCPAP. Approximately 32 subjects will be randomized to the control arm and will receive nCPAP alone.

2.2.1 Capillary-based Aerosol Generating Systems

Newer technologies, such as the CAG system, may allow for administration of aerosolized surfactant to preterm neonates in sufficient quantities to affect a therapeutic response similar to the response demonstrated in surfactants administered by endotracheal instillation. A device that permits effective surfactant aerosolization to neonates receiving nCPAP support for the treatment of RDS may improve the success of nCPAP therapy.

2.2.2 Rationale for Study Control

The use of nCPAP in the US is widely utilized for the treatment of RDS in preterm newborns, and current guidelines outline several patient interface devices that can be used to deliver continuous airway pressure such as nasal masks, short bi-nasal prongs, and nasopharyngeal tubes[4]. Thus, preterm neonates who, in accordance with current treatment practice, would be treated with nCPAP are appropriate controls for this study.

2.2.3 Dose Rationale

Lucinactant, administered as an intratracheal 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 infants at high risk for RDS. Infants at high risk for RDS are presumed to be substantially or wholly surfactant deficient and require endotracheal intubation and mechanical ventilation. In contrast, the population of preterm infants who can be sustained by nCPAP, rather than endotracheal intubation and mechanical ventilation, likely represent a broad spectrum of varying degrees of surfactant insufficiency. While infants born at a lower gestational age are likely to be more surfactant insufficient compared with infants born at higher gestational ages, a myriad of factors can also influence these degrees of surfactant insufficiency. Therefore, dosing algorithms based on gestational age, or birth weight as a surrogate for gestational age, would not necessarily represent the optimal method for estimating the dose of surfactant that should be administered to adequately treat RDS. Nevertheless, preterm infants who can be sustained by nCPAP are unlikely to require a full replacement dose of SRT. Thus, it is likely that preterm

infants on nCPAP will require substantially less than the intratracheal bolus dose of 175 mg TPL/kg of lucinactant. In fact, based on a previously conducted clinical study of aerosolized lucinactant (KL4-CPAP-01), the target theoretical inhaled dose is likely to be in the range of 75 mg TPL/kg or higher.

The relative inefficiency of inhalation therapy must also be considered. Due to the viscoelastic properties of surfactant, it is highly likely that most, if not all, of the surfactant delivered as a bolus to the trachea will ultimately arrive in the alveoli, the site of action for surfactant. However, the entrainment of surfactant administered as an aerosol into the subglottic airway to the nasopharynx will vary depending on the characteristics of the aerosol, such as particle size and rate of administration, and the breathing characteristics of the individual neonate (eg, inspiratory and expiratory patterns, frequency, and tidal volume). The aerosol particle size and rate of administration can be kept constant; however, the rate of administration should be representative of the infant's inspiratory flow to optimize the efficiency of aerosol entrainment. Typically, inspiratory and expiratory patterns in preterm infants will vary from breath to breath. However, breathing frequencies and tidal volumes are less variable in preterm populations. Minute ventilation, which is related to body surface area and therefore indirectly related to body weight, is the product of frequency and tidal volume. Therefore, minute ventilation can be used to estimate the theoretical maximum inhaled dose of aerosolized surfactant normalized to body weight. The actual inhaled dose is likely to be less since some aerosolized surfactant will be expelled during exhalation or will deposit in the oropharynx and be swallowed into the stomach.

The safety of the total TPL load and volume of fluid that infants will receive (and any potential for impact on serum electrolytes and acid-base balance) is supported both by prior toxicology studies and by preclinical and clinical experience.

2.2.3.1 Preclinical 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 lavage 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 non-clinical animal toxicology studies in pre-weaned rabbits (N107662) and pre-weaned rats (N107663) evaluated the acute toxicity of inhaled lucinactant (aerosolized by

CAG technology). Rabbits and rats were exposed to aerosol on 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 NOAELs were established to ensure adequate safety in preterm neonates.

Preclinical studies provide a safety margin of > 15:1 for the highest dose (150 mg TPL/kg), whether delivered to the lungs (> 2700 mg TPL/kg) or swallowed (8400 mg TPL/kg) (including volume load and sodium load).

2.2.3.2 Clinical Experience Supporting Dose Rationale

Human subjects have been exposed to both high doses and large volumes of lucinactant administered by intratracheal bronchial lavage. In addition, study populations consisting of neonates with meconium aspiration syndrome and adults with acute respiratory distress syndrome have received doses up to 1710 ml[12,13].

In addition, lucinactant for inhalation in doses up to 75 mg TPL/kg has been administered in Study 03-CL-1201 in infants 29 to 34 weeks PMA. Currently, subjects are being enrolled into the extension phase of the study (Dose group IV; 100 mg TPL/kg or control). This study (03-CL-1401) includes the same entry criteria and the same assessments at the same evaluation times.

Protocol 03-CL-1201

Doses of lucinactant for inhalation up to 150 mg TPL/kg have been administered and the safety and tolerability drug-device combination product reviewed by an independent safety committee. Through doses up to 100 mg TPL/kg, lucinactant for inhalation appears generally safe and tolerated with no specific safety issues noted. Preliminary information suggests that 25 mg TPL/kg may be a sub-therapeutic dose based on physiological assessments compared with the nCPAP control group; as a result, the proposed starting dose for neonates with a greater degree of surfactant insufficiency is 50 mg TPL/kg for this study (03-CL-1401).

Primary safety and tolerability measures include survival, air leak, complications of prematurity, and AEs. In addition, assessments on vital signs, PCO_2, FiO_2, serum electrolytes, and gastric

liquid volume will be performed. A summary of selected measures is provided in the Aerosurf investigator's brochure.

To date, one death has occurred; the subject expired 9 days following aerosolized lucinactant administration of 150 mg/kg due to sudden, unexplained, cardiopulmonary deterioration not related to study drug or study protocol. All subjects randomized received study treatment. No clinically meaningful difference between any of the active groups and the nCPAP Only group have been observed for complications of prematurity, though sample sizes are small.

There appeared to be a higher rate for several AEs, including airleak, in the Group I active group compared with the control group; however, small numbers make these comparisons difficult. Moreover, data for Dosing Groups II, III, and IV do not suggest clinically relevant areas of concern. The most common type of air leak reported has been pneumothorax. No clinically relevant differences have been observed between the active groups and the control group on completion of dosing Groups II, III, and IV.

The subjects in the active and control groups exhibit results for serum electrolytes that are very similar, indicating that the investigational product has had no demonstrable impact on serum electrolytes.

In summary, the preliminary data for Protocol 03-CL-1201 indicate that there are no specific safety concerns and that the doses studied are generally safe and tolerated. The SRC has reviewed all safety data from Dosing Groups I through IV, and in each case recommended that the study continue. The results also indicate that the dose of 25 mg TPL/kg is likely a subtherapeutic dose. After evaluation of the data by the steering committee and discussion with Discovery, it was determined that the appropriate starting dose of for this study (03-CL-1401) should be 50 mg TPL/kg.

2.2.3.3 Dose Exposure and Delivery

The inhaled doses for this dose escalation study are based on a previously conducted clinical study of aerosolized lucinactant (KL4-CPAP-01) that consisted of a theoretical inhaled dose of aerosolized lucinactant 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). The initial dose will be approximately one third of the theoretical inhaled dose of the previous study.

The theoretical inhaled dose can be estimated using the following equation:

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

Where: C = Aerosol concentration
Vm/kg = Minute ventilation per kg of body weight
T = Dose duration in minutes

- C: the aerosol concentration is calculated by dividing the emitted dose by the flow rate of the carrier gas used to drive the aerosol to the patient interface;
- Vm/kg : the subject's Vm can be calculated based on the patient's weight[14], or based on direct neonatal lung function measurements of newborns[15]. Table 2.2-1 shows the comparison of Vm values derived from these two sources;
- T: the duration of aerosol exposure in minutes is a modifiable, external factor that is determined by the target inhaled dose as a function of the CAG output; once this is known, the nominal dose can be calculated.

The emitted dose of the ADS is the product of the CAG output (1.2 ml/min), the concentration of the lucinactant (30 mg TPL/ml) and the fraction of the nominal dose that is delivered at the patient interface is 0.35:

Emitted dose = 1.2 ml/min x 30 mg TPL/ml x 0.35 = 12.6 mg TPL/min

The aerosol concentration (C) is the emitted dose (12.6 mg TPL/min) divided by the carrier gas flow rate (3 L/min). This flow rate was chosen because it best represents the range of inspiratory flow rates observed in the target population.

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

Estimates of minute ventilation (Vm) within the range of body weights of preterm infants expected to enroll in the study are listed in Table 2.2-1, based on the work of Bide, et al. and Bhutani, et al [14,15]. When normalized to body weight, the Vm/kg is consistent across the range of weights at approximately 0.4 L/min/kg.

Table 2.2-1. Minute Ventilation Comparison Between Bide and Bhutani

	Bide et al.		Bhutani et al.	
	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 four levels for the theoretical inhaled dose are 50, 75, 100, and 150 mg TPL/kg. By using these values, the dose duration (T) is calculated by dividing the target inhaled dose by the product of C (4.2 mg TPL/L) and Vm (0.4 L/min/kg). This calculation yields dose durations of 30, 45, 60 and 90 minutes to achieve target theoretical doses.

2.2.3.4 Dose Durations

The dosing duration for the 50 mg/kg, 75 mg/kg, 100 mg/kg, and 150 mg/kg inhaled doses have been established at 30, 45, 60, and 90 minutes.

Table 2.2-2 provides a summary of the dosing durations for each dosing group. Calculations used to derive these aerosolization times are outlined in this section.

Table 2.2-2. Dosing Duration in Minutes for Each Dosing Group

	Dose and Dosing Time (min)			
Weight (g)	50 mg/kg	75 mg/kg	100 mg/kg	150 mg/kg
750 – 2750	30	45	60	90

Note: Based on Bhutani, et al. [15]

Neonates of low weight will receive slightly more study drug, while those with a higher weight will receive slightly less.

2.3 Study Duration

It is expected that recruitment will occur over a period of 7 months, with an average of 1 subject enrolled per 4 weeks for each of the approximately 12 study sites (actual subject recruitment period may vary). It is estimated that the last subject enrolled will complete all assessments and procedures within 9 months from the time of the first subject enrolled. Thus the total duration of the study is expected to be approximately 9 months.

Any adverse findings by the SRC may result in early study closure and early withdrawal of study subjects **(**Section 6).

2.3.1 Duration of Subject Study Participation

The total duration of study participation for each subject will be from enrollment (≤ 20 hours from birth) to 36 weeks PMA. All subjects who complete all assessments and procedures up to and including the Final Visit (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 periods (assessments, procedures, and visits associated with each of these phases can be found in Section 7.1):

- 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.
- Primary Observation Period: time of randomization (T_0 on study) to 48 hours from randomization.
  - To include: pre-treatment assessment, treatment period (30, 45, 60, or 90 minutes), followed by continual safety monitoring in accordance with local NICU procedures.
  - Study treatment must be initiated ≤ 22 hours from the time of birth
- Extended Observation Period: > 48 hours on study to completion on Study Day 7 (6 days after the day of randomization by calendar date) or until time of death or hospital transfer/discharge, whichever comes first.
- Final Observation Period: ≥ Study Day 8 to 36 weeks PMA or discharge or until of death or hospital transfer/discharge, whichever comes first.

3 STUDY OBJECTIVES AND ENDPOINTS

This study is designed to investigate the safety and tolerability of lucinactant for inhalation in preterm infants of gestational age 26 to 28 completed weeks PMA. Safety and tolerability will be based on clinical evaluations (Section 8). Efficacy will be an exploratory objective. The endpoints specified are the same endpoints as Protocol 03-CL-1201, to allow for potential comparison and pooling of results.

3.1 Primary Objective

The primary objective of this study is to evaluate the safety and tolerability of lucinactant for inhalation, administered as an aerosolized dose in 4 escalating doses to a preterm, neonatal population 26 to 28 completed weeks PMA receiving nCPAP for RDS compared with neonates receiving nCPAP alone.

Safety and tolerability will be evaluated using the same measures and assessments that have been used in Protocol 03-CL-1201, which has shown lucinactant for inhalation up to 75 mg/kg to be generally safe and well-tolerated in infants 29 to 34 completed weeks PMA.

3.1.1 Primary Endpoints

The primary endpoints of this study will be derived from the safety evaluations, including adverse device effects (ADEs) reported from the time of randomization until 36 weeks PMA of upon discharge (Section 3.3).

3.2 Secondary Objective

The secondary objective of this study is to determine the maximum tolerated dose of lucinactant as determined by the safety evaluations obtained within each dosing group (Section 3.3), and to assess the feasibility of evaluating physiological pulmonary function parameters as a measure of improvement in clinical status (Section 3.4) in preterm infants 26 to 28 completed weeks PMA who are receiving nCPAP for RDS, compared with preterm infants receiving nCPAP alone.

3.3 Safety Evaluations

The following measures are to be documented in the electronic case report form (eCRF) in accordance with timings outlined in Appendix 2 and Section 7:

1. Survival (date and time of death if applicable)

2. AEs, including ADEs
    - To include: nasal excoriations by examination (≥ 24 hours to ≤ 7 days following aerosol exposure) and evidence of lung air leak (especially pneumothorax) (Section 7.1.8)
    - To be categorized as a peri-dosing events if onset of event is ≤ 2 hours from the time of initiating administration of lucinactant for inhalation [Section 9])
3. Signs consistent with worsening respiratory status (Section 7.5)
4. Concomitant medications (Section 7.3)
5. Use of respiratory support and supplemental oxygen (Section 7.6), to include:
    - Need for endotracheal intubation and mechanical ventilation
    - Need for intermittent positive pressure breaths using inflating pressures above the set CPAP pressure administered manually or mechanically through any patient interface
    - nCPAP and fraction of inspired oxygen (FiO_2) requirements (Section 5.4.1), (Section 7.6.2)
6. Complications of prematurity (ie, IVH, periventricular leukomalacia [PVL], pulmonary hemorrhage, NEC, patent ductus arteriosus [PDA], sepsis, ROP, BPD)
7. Physical examinations (Section 7.1.6)
8. Tolerability of lucinactant for inhalation
9. Incidence leading to withdrawal from study
10. Incidence of air leak
11. Assessments of the following:
    a) PCO_2 (Section 7.1.5)
    b) Serum electrolyte measurements (Section 7.1.7)
    c) Body weight (Section 7.1.2)
    d) Vital signs (Section 7.1.1)
    e) Gastric liquid volume (Section 7.1.9)
    f) Defecation (Section 7.1.10)
    g) Oxygen (O_2) saturation, as determined by pulse oximetry (SpO_2) (Section 7.1.3)
    h) Chest radiography, as applicable (Section 7.1.8)

3.4 Exploratory Efficacy Objective

To demonstrate the ability to measure clinical effect.

3.4.1 Efficacy Endpoints

Exploratory efficacy endpoints will be evaluated from the time of lucinactant for inhalation initiation until study completion (non-hypothesis testing) and will include the following:

1. Incidence of BPD
2. Rate of survival without BPD at 36 weeks PMA or upon discharge
3. Worsening of respiratory status (Section 7.5)
4. Technical performance of the ADS
    - The efficacy of the device delivery of lucinactant for inhalation will be characterized indirectly through the subject's response to treatment and solicited feedback from the PIs and relevant site-based study staff.
5. Physiological parameters (eg, FiO_2, PCO_2)

4 STUDY POPULATION SELECTION

4.1 Study Population

The study population will consist of approximately 64 preterm neonates from 26 to 28 completed weeks PMA with RDS who are candidates for SRT and nCPAP in a NICU setting. A subject will be enrolled at 1 of approximately 25 study sites in the US.

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;
2. Gestational age 26 to 28 completed weeks PMA;
3. Successful implementation of controlled nCPAP within 90 minutes after birth;
4. Spontaneous breathing;
5. Chest radiograph consistent with RDS; and
6. Within the first 20 hours after birth, requires an nCPAP of 5 to 6 cm H2O to maintain SpO2 of 88% to 95% with an FiO_2 of 0.25 to 0.50 that is clinically indicated for at least 30 minutes. Transient (<10 minutes) FiO_2 excursions below 0.25 or above 0.50 do not reset the 30 minute 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 beats/minutes within 5 minutes of birth;
2. Recurrent episodes of apnea occurring after the initial newborn resuscitation period (ie, 10 minutes after birth) requiring intermittent positive pressure breaths using inflating pressures above the set CPAP pressure administered manually or mechanically through any patient interface;
3. A 5-minute Apgar score < 5;
4. Major congenital malformation(s) and cranial/facial abnormalities that preclude nCPAP, diagnosed antenatally or immediately after birth;
5. Other diseases or conditions potentially interfering with cardiopulmonary function (eg, hydrops fetalis or congenital infection such as TORCH);
6. Known or suspected chromosomal abnormality or syndrome;

7. Premature rupture of membranes (PROM) > 2 weeks;
8. Evidence of hemodynamic instability requiring vasopressors or steroids for hemodynamic support and/or presumed clinical sepsis;
9. A need for endotracheal intubation and/or mechanical ventilation; and
10. Has been administered any the following:
    a) Any investigational agent or exposure to a medical device,
    b) Any other surfactant agent, or
    c) Steroid treatment (steroid exposure before birth is acceptable).

Note: All subjects must continue to meet entry criteria at the time of initiation of study therapy.

5 STUDY DOSING AND ADMINISTRATION

Preterm neonates between 26 and 28 completed weeks PMA who are within the first 20 hours after birth and who had successful implementation of controlled nCPAP within 90 minutes of birth will be considered to be potential subjects. 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 (eg, FiO_2, heart rate, O_2 saturation) 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. As soon as study eligibility has been confirmed and the informed consent is signed, subjects will be randomized. All study subjects are to be randomized within 20 hours after birth to either an active study arm or a control arm. Subjects randomized to an active arm will receive 1 dose of lucinactant for inhalation, initiated within 2 hours of randomization through the investigational ADS device administered over 30, 45, 60, or 90 minutes in conjunction with nCPAP support. One additional treatment is allowed if subjects meet the repeat dose criterion. Subjects randomized to a control arm will be continued on nCPAP alone.

If at any point during the delivery of lucinactant for inhalation, a potential safety risk to the subject is identified, aerosolization must be discontinued by activating the ADS 'Stop Treatment' interface. Local NICU procedures should be followed in the event of early discontinuation of lucinactant for inhalation to ensure the safety and care of the subject. Any significant clinical findings or observations must be documented and communicated to Discovery at the earliest time point possible.

5.1 Precautions for Aerosol Delivery and Device Usage

The ADS, disposables, and study drug are investigational materials, and are to be used only for lucinactant for inhalation investigational studies, and are not to be used for 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 ADPs). Details on study supply accountability and storage are provided in Section 5.6 and in the ADS Operator's Manual.

The PI or study-trained designee must provide close monitoring of the subject and study device during aerosol delivery.

5.1.1 Precautions for Aerosol Delivery

The device and interface used for nCPAP delivery during aerosol delivery must be commercially available for nCPAP delivery to neonates. During the nCPAP delivery, subjects must be closely monitored for complications related to placement of the patient interface. Assessment must include, but not be limited to, evaluations for the following conditions: bleeding, apparent obstruction of the nares, occlusion of interface requiring removal and replacement, nasal irritation (erythema of nares or septum, inflammation of nares or septum).

Local NICU policies and procedures for nCPAP delivery are to be used to deliver both the study drug and nCPAP, regardless of randomization (ie, active arm or control arm). After connecting the aerosol tube to the CPAP adapter and initiating aerosolization, the PI must ensure that the desired CPAP is maintained. During the dosing period, the subject's head should be securely but gently immobilized. Pacifiers can be used during dosing periods.

5.1.2 Stopping Criteria for Aerosol Delivery

The administration of lucinactant for inhalation may be discontinued at any time in accordance with the clinical judgment of the PI or the wishes of the subject's legal guardian. In accordance with local institutional practices, a proven SRT must be made available to subjects demonstrating a clinical need following exposure to lucinactant for inhalation. Reasons for discontinuation of lucinactant for inhalation may be related to but not limited to the following:

1. Device failure or malfunction, including error codes or treatment interruptions;
2. Pulmonary hemorrhage or other AE/ADE;
3. In the PI's best medical judgment, initiating or continuing the subject's exposure to lucinactant for inhalation is not in the best interest of the subject's safety, such as hemodynamic instability. (Note: When medical judgment is the sole criteria for stopping therapy, a detailed narrative describing the clinical events and observations supporting the decision to stop therapy needs to be documented.);
4. Signs of respiratory deterioration as evidenced by an increased respiratory rate or an observed increase in respiratory effort (work of breathing) plus at least one of the following:

    - An $FiO_2 \geq 0.70$ or a sustained ($\geq$ 10 minutes) increase from baseline by ≥ 0.30 to maintain oxyhemoglobin saturation ($SpO_2 \geq 88\%$),

- A $PCO_2 > 70$ mm Hg or a progressive increase in PCO_2 from baseline to ≥ 20 mm Hg above baseline and confirmed with a blood gas,
- Recurring episodes of bradycardia defined as a heart rate of < 100 bpm for ≥ 20 seconds,
- A sustained apneic event, defined as apnea at least 20 seconds in duration and meeting at least one of the following: (1) HR < 100 bpm, (2) desaturation (oxygen saturation < 80%), (3) requirement for IPP breaths using inflating pressures above the set CPAP pressure administered manually or mechanically through any patient interface.

5.1.3 Precautions for Device Usage

Before aerosol activation with the ADS, 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, to include any emergent or routine medical needs of the subject during and following aerosol delivery with the device.

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 immediately contact the clinical site monitor and call Discovery's reporting line (855-4ACTADS [855-422-8237]). A representative from Discovery will call with further instructions. In such cases, the subject should 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 be indicate delivery failure.

5.1.4 Assessment Parameters for Technical Performance of the Device

The following parameters will be captured in the eCRF:

1. Any issues associated with device tubing (eg, ventilator/CPAP tubing detachments, aerosol tube detachments, proximal pressure port obstruction, aerosol tube condensate obstruction).
2. Approximate volume (in ml) of liquid in all the traps.

3. Aerosol or study drug leakage before the subject interface (eg, disconnect of the inspiratory circuitry).
4. Occurrence of alarm signals before, during, or after dosing that may indicate a device malfunction.
5. Any automatic system shutdowns.
6. Loss of inspiratory flow to the neonate or inability to maintain nCPAP.
7. ADS temperature alerts (high or low).

5.2 Description of Study Assignment and Aerosol Delivery

The study treatment, 'lucinactant for inhalation,' consists of the investigational drug lucinactant and the delivery system ADS. The ADS has two components, the Aerosurf® Delivery Pack (ADP) and the Aerosurf® Control Unit (ACU). The rationale for the selected treatment and device technology is discussed in Section 2.2.

5.2.1 Aerosol Delivery

Preterm neonates between 26 and 28 completed weeks gestational age who are within the first 20 hours after birth and who had successful implementation of controlled nCPAP within 90 minutes of birth will be considered to be potential subjects. 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 (eg, FiO_2, heart rate, O_2 saturation) 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 may be performed until the informed consent has been provided by a legally authorized representative of the subject. As soon as study eligibility has been confirmed and the informed consent is signed, subjects will be randomized. All study subjects are to be randomized within 20 hours after birth to either an active study arm (consisting of lucinactant for inhalation in conjunction with nCPAP) or a control study arm (consisting of nCPAP alone).

Details for study drug preparation are provided in the Aerosurf Investigator's Brochure and in the ADS Operator's Manual. Briefly, 10 ml of sterile water for injection are added to each of 7 vials and the vials are gently inverted to mix the suspension. A total of approximately 60 ml of solution are drawn up into the provided ADP syringe, which is loaded into the ACU.

Study treatment is to begin within 2 hours after randomization. For subjects randomized to the active study arm, the treatment dose (ie, drug exposure) will be 50, 75, 100, or 150 mg

TPL/kg (delivered over 30, 45, 60, or 90 minutes, respectively) in accordance with the subject's dosing group. A repeat dose at the same level is allowed if the repeat dosing criterion is met (see Section 5.2.5).

The carrier gas flow rate for the ADS is 3 L/min. This is consistent with the anticipated peak inspiratory flow (PIF) of preterm neonates (between 26 and 28 weeks PMA) and therefore will reduce potential aerosol dilution.

A summary of dose selection for this study is provided in Section 2.2.3.

5.2.2 Study Assignment; Dosing Groups

Subjects will be assigned to 1 of 4 dosing groups (Table 5.2-1).

Table 5.2-1 Study Assignments by Dosing Groups

Dosing Group	Study Assignment
Dosing Group I	Active Arm: (n = 8 subjects) Lucinactant for inhalation: 50 mg TPL/kg administered over 30 minutes with nCPAP 1 repeat dose is allowed if repeat dosing criteria are met Control Arm: (n = 8 subjects) Continuous nCPAP
Dosing Group II	Active Arm: (n = 8 subjects) Lucinactant for inhalation: 75 mg TPL/kg administered over 45 minutes with nCPAP 1 repeat dose is allowed if repeat dosing criteria are met Control Arm: (n = 8 subjects) Continuous nCPAP
Dosing Group III	Active Arm: (n = 8 subjects) Lucinactant for inhalation: 100 mg TPL/kg administered over 60 minutes with nCPAP 1 repeat dose is allowed if repeat dosing criteria are met Control Arm: (n = 8 subjects) Continuous nCPAP
Dosing Group IV	Active Arm: (n = 8 subjects) Lucinactant for inhalation: 150 mg TPL/kg administered over 90 minutes with nCPAP 1 repeat dose is allowed if repeat dosing criteria are met Control Arm: (n = 8 subjects) Continuous nCPAP

Note: Eligible subjects 26 to 28 weeks PMA will be randomized into either the active or control arm in accordance with the dosing group enrolling at the time of subject randomization:

5.2.3 Method of Assigning Study Subjects to Dosing Groups

For each dosing group, preterm neonates who successfully meet all eligibility criteria within the enrollment period (20 hours) will be randomly assigned to 1 of 2 study arms (active or control) (Section 5.2.2). Subjects will be randomized using centralized allocation by an interactive web response system (IWRS). Infants from multiple births will be randomized independently.

The randomization code list will be generated by Discovery Biometrics personnel and transmitted to the IWRS vendor. The code list will use a block size of 4 for each dosing group.

5.2.4 Sequential Dosing Scheme

The study dosing will initiate in Dosing Group I (the lowest dose), and continue to Dosing Group II after completion of enrollment. Each dosing group will enroll sequentially following completed enrollment of the previous dosing group. After all active subjects within each dosing group have completed 72 hours, the SRC will review the safety and tolerability of this dose.

If there appears to be intolerability with a given dose or operational challenges administering a dose, the remaining subjects may have the dose decreased to a previously administered dose, after consultation with the SRC.

Further details on the dosing for each dosing group are provided in Section 5.2.2.

5.2.5 Repeat Dosing

In order to ensure the safety of repeat dosing, specifically in regards to AEs and electrolyte changes (such as sodium and potassium levels), and to ensure subjects with a demonstrated need receive treatment, 1 repeat dose will be allowed for all dosing groups. The repeat dose will consist of repeating the same dose and will occur between 2 and 24 hours after the initial dose, if the repeat dosing criterion is met. The repeat dosing criterion is defined as at least 2 hours, but no more than 24 hours, after dosing and the subject must require a sustained need for supplemental oxygen at or above the qualifying FiO_2 level for study entry (ie, 0.25) for at least 30 minutes to maintain SpO_2 of 88% to 95%.

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

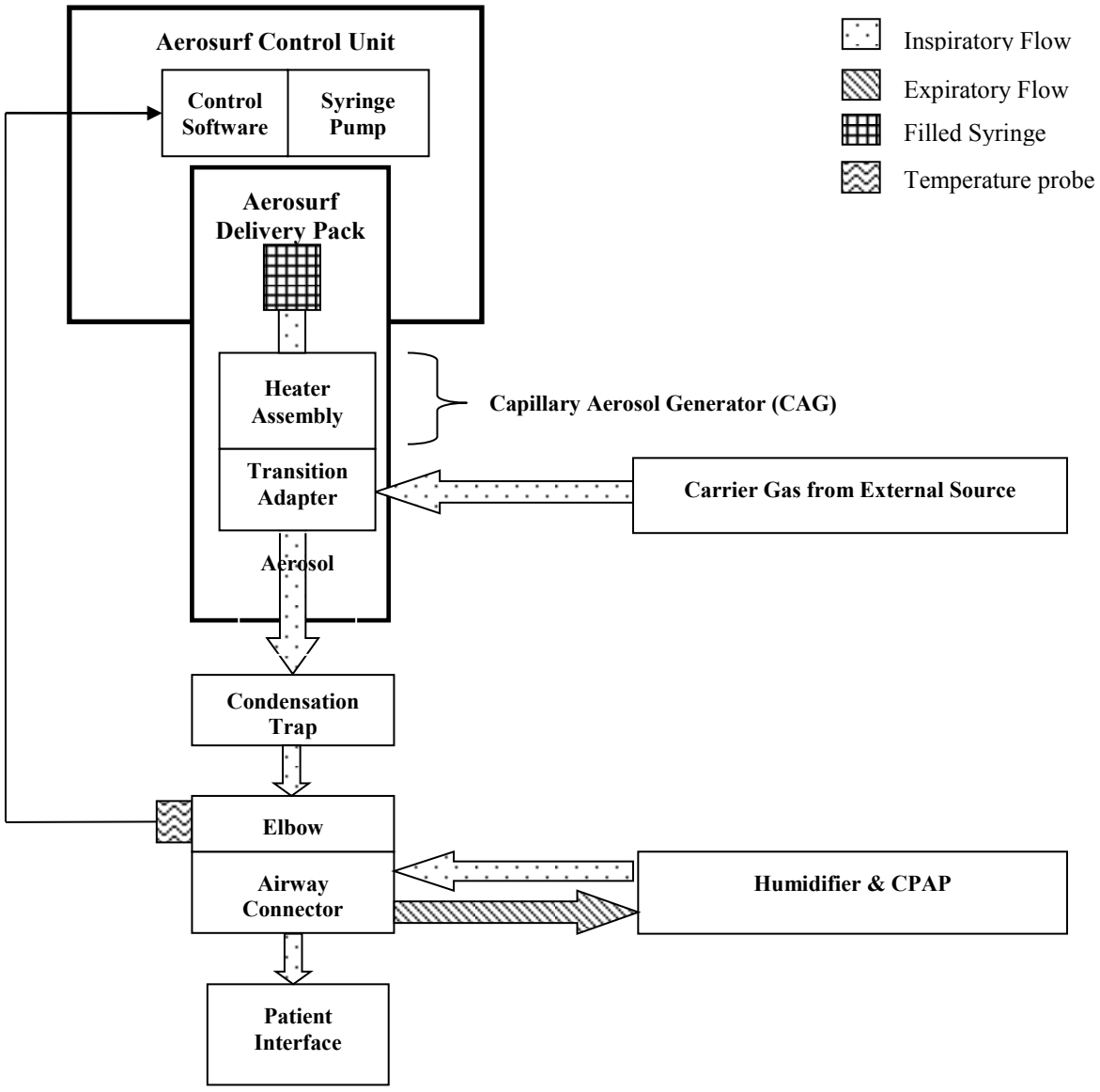
If, in the opinion of the PI, repeat dosing would compromise the safety of the subject, repeat dosing will not occur.

5.3 Aerosurf Delivery System

The ADS creates and controls aerosolized surfactant (lucinactant for inhalation) through 2 components, the ACU (Section 5.3.1) and the disposable ADP (Section 5.3.2). At the patient interface, two external flow sources are combined: humidified air from the CPAP system and carrier gas flow from the ADS (Figure 5.3-1). The entire ADS is a device designed for bedside use, and is mounted on a wheeled cart for easy transport.

A complete qualitative risk assessment has been completed to identify and mitigate potential safety risks associated with use of the ADS.

Figure 5.3-1. Aerosol Delivery System



The ADS produces the aerosolized form of lucinactant through heat and pressure created within the CAG located within the heater assembly. The ADP is in-line to the ACU, and jointly these two components produce, control and monitor the key elements necessary for the production of aerosolized surfactant (lucinactant for inhalation). A summary of the key functions each of the

ADS components (ACU and ADP) contributes to the aerosolization of lucinactant is provided in Table 5.3-1.

Table 5.3-1 Key Function of Aerosurf Control Unit and Aerosurf Delivery Pack

Key Component	Aerosurf Control Unit	Aerosurf Delivery Pack
Carrier Gas[1]	N/A	Contains the carrier gas tube assembly that is connected to an external gas source[1].
Heater	Measures and controls the heater, which enables aerosol generation	Contains the heater assembly, placed in line with the Aerosol Control Unit to heat lucinactant for inhalation.
Lucinactant	Contains a chamber with a locking door mechanism to accept the filled syringe; prevents access to syringe chamber after aerosolization is started.	Includes a 60 ml syringe, which is filled to the maximum volume with lucinactant for inhalation.

[1] Carrier gas is an external flow source of oxygen and room air blends, at percentages that are in accordance with the study protocol, subject safety, and best medical judgment as directed by the PI.

5.3.1 Aerosurf Control Unit

The ACU contains a syringe pump mechanism integrated with control electronics and a temperature probe. The control electronics consists of embedded hardware and software with a touch screen interface that provides sequential instruction for (1) ADS set-up, (2) system operation, (3) safety interventions, and (4) temperature control. A cart is provided for use with the ACU. Materials and dimensions for the ACU are consistent with similar equipment used in critical care environments.

5.3.2 Aerosurf Delivery Pack

The ADP is a single-use, disposable pack containing a 60 ml syringe, the tube assembly, and the heater assembly. A summary of the ADP functions are provided in Table 5.3-1.

5.3.2.1 ADP Set-up

Instructions for the proper set-up and connections of ADP components are provided in the ADS Operator's Manual. Depending upon the dose, 1 or 2 ADPs will be required for each treatment.

The syringe is filled to maximum volume with the lucinactant suspension and placed in the syringe sleeve located in the ACU. To ensure full aerosol delivery, and proper functionality of

the device, it is imperative that the syringe is filled to the maximum volume and all air bubbles are removed before placement into the device.

5.3.2.2 ADP Post Delivery Procedures

The ADP must be disengaged from the ADS and returned to Discovery after completion of aerosol delivery (as indicated on the ACU screen). All fluid should be removed from the aerosol tubing and fluid traps in accordance with local institutional practices before shipping.

Instructions on proper removal of the ADP from the ADS are provided in the ADS Operator's Manual.

Study ADPs are required to be returned to 1 of 3 return facilities in accordance to the following categories.

1. Unused ADPs are shipped to Battelle at the time of site closure or at the request of Discovery (clinical site monitors will provide additional information to study sites on associated shipping procedures and addresses);
2. Used ADPs that are not associated device errors are picked-up by a specified vendor for destruction;
3. ADPs associated with device errors are shipped to Battelle, when requested by Discovery (further information regarding associated shipping procedures is made available to study sites at the time of the request).

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

5.4 Delivery of On-Study Continuous Positive Airway Pressure

The use of nCPAP will be implemented within 90 minutes of birth. On-site study staff will be trained on the use and functionality of the nCPAP device for use during this study. The nCPAP device and training will be provided by Discovery or qualified designee.

The use of nCPAP can be preceded by intermittent positive pressure breaths using inflating pressures above the set nCPAP pressure administered manually or mechanically through a non-invasive patient interface (mask, nasal prongs) for no longer than 10 minutes after birth (eg, NeoPuff).

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 closely monitored for complications related to placement of the patient interface (eg, bi-nasal prongs). Assessment must include but not be limited to evaluations for the following conditions: bleeding, apparent obstruction of the nares, occlusion of interface requiring removal and replacement, nasal irritation (erythema of nares or septum, inflammation of nares or septum).

5.4.1 Set-up of Continuous Positive Airway Pressure System

The CPAP Operator's Manual provides details on the proper set-up and operation of the nCPAP device. These procedures, in conjunction with local institutional practices, must be followed to optimize subject safety, and to ensure consistent, therapeutic pressure that minimizes resistance in the artificial and preterm infant airways.

The essential procedures to further minimize resistance during nCPAP delivery are as follows:

1. Ensure proper placement of the patient interface

   Note: the device and subject interface used for nCPAP delivery during aerosol delivery must be commercially available and specifically for nCPAP delivery in neonates
2. Insert a gastric tube (open to air) after proper placement of the patient interface has been assessed.
3. Maintain the subject's neck position in a mild extension that is comfortable for the subject
4. Assess the need for nasal and oral airway suctioning and administer as needed

5.4.1.1 Initial nCPAP Settings

The initial nCPAP settings will depend on the subject's clinical condition and may be adjusted in accordance with Section 5.4.1.2; however, the following are the recommendations for initial nCPAP settings:

- $FiO_2 \geq 0.25$ (based on inclusion criteria met; refer to Section 4.2) and < 0.50 (Section 7.6)
- CPAP = 5 to 6 cm H_2O

5.4.1.2 Adjustments to nCPAP Settings

Incremental increases in nCPAP should be made by 1 cm H_2O until a maximum nCPAP of 6 cm H_2O is achieved and the following subject parameters are maintained for the duration of aerosol administration:

- $SpO_2 \geq 88$ and $\leq 95\%$
- $FiO_2 \geq 0.25$ and < 0.50 (Section 7.6)
- $PCO_2 < 50$ mm Hg (Section 7.1.5)
    - If a sustained nCPAP of ≥ 7 cm H_2O is necessary to maintain SpO_2 88 to 95% or $PCO_2 > 50$ mm Hg, then the subject should be evaluated for clinical signs and symptoms consistent with worsening of respiratory status (Section 7.5).

5.4.1.3 Documentation of nCPAP Settings

nCPAP settings must be documented in the study eCRF at the time of initial randomization and at the following timeframes: 1, 3 (± 15 minutes), 6, 12 (± 1 hour), 18, 24, 36, and 48 hours (± 2 hours) after randomization.

5.5 Identity of Investigational Drug Product

The complete list of ingredients for the drug product is shown in Table 5.5-1.

5.5.1 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 dipalmitoyl-phosphatidylcholine (DPPC) and palmitoyloleoyl-phosphatidylglycerol, sodium salt (POPG, Na), and the fatty acid palmitic acid (PA). Immediately before dosing, the lyophilized product is reconstituted with sterile water for injection at a concentration of 30 mg TPL/ml.

Table 5.5-1. 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/ml

5.5.1.1 Aerosol characteristics

The aerosol is generated at a formulation flow rate of approximately 20 µL/second. The mass median aerodynamic diameter (MMAD) of the aerosol is below 5.0 µm. The ventilated gas that carries the aerosol to the subject has a nominal flow rate of 3 L/minute. A disposable fluid trap collects the condensed aerosol that is not transferred to the ventilation circuit (Figure 5.3-1). The specification for the aerosol temperature at the patient interface is 25°C to 38°C.

5.5.2 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 required FDA caution statements, to insure that users are aware that the product is limited by federal law to investigational use only.

5.6 Clinical Study Supplies at the Clinical Study Site

5.6.1 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.

5.6.2 Ancillary Supplies

Ancillary supplies (eg, CPAP system, nasal prongs, 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.

5.6.3 Dispensing

Study supplies (study drug, ADP, and related study equipment) will be dispensed in accordance with the subject's randomized dosing group (Section 5.2.2). The NICU pharmacist or designated study personal 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.

5.6.4 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.

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.

5.7 Study Compliance

Study compliance will be based on the actual delivery time of lucinactant for inhalation in comparison to the subject's randomized aerosolization time. Aerosolization time will be tracked by the ACU, which will display a continual count of lucinactant exposure time throughout the aerosol delivery period. The length of lucinactant exposure time (as observed through aerosol delivery and ACU display) will be documented in the study eCRF. The ACU will also display an interface to allow for emergent aerosol discontinuation. PIs are to discontinue aerosol delivery if a potential safety risk to the subject is identified at any point during the aerosol delivery period.

The number of subjects randomized but not treated, and the number of subjects prematurely discontinued from aerosol delivery will be recorded in the eCRF and summarized in the study report.

No diaries will be required since lucinactant for inhalation will be administered at the clinical site.

5.8 Study Drug and Device Accountability

It is the responsibility of the PI and trained 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.

5.8.1 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 study aerosol delivery.
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 SAFETY REVIEW COMMITTEE

The purpose of the SRC is to evaluate the degree of risk involved in study subject participation within each dosing group 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 the time all active subjects in each dose group completes assessments and procedures through 72 hours.

The SRC 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 SRC 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).

Following a thorough independent review of available study data, the SRC will provide timely recommendations to the Discovery study team. Recommendations may consist of, but not be limited to the following:

- Continue enrollment at the next higher dose level, which includes a potential repeat dose,
- Suspend or close study enrollment

At each review, the control subjects will be summarized in aggregate.

An 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, if more than 2 subjects per dosing group experience an SAE related to dosing, enrollment and dosing will be suspended and further enrollment and dosing will proceed only if and when the SRC deems it to be appropriate.

In addition, if a treated subject dies during the first 12 hours following and related to lucinactant for inhalation administration, then an unscheduled meeting of the SRC will be called. Safety and

tolerability data will be presented to the SRC for their immediate review. Study enrollment will be suspended until such time that a safety assessment has been completed. Enrollment and dosing will proceed only if and when the SRC deems it to be appropriate. If the SRC deems it to be appropriate to re-initiate enrollment after an enrollment hold, IRB approvals will be obtained before the re-initiation of subject screening and enrollment activities.

7 STUDY PROCEDURES AND GUIDELINES

A Schedule of Events representing the required testing procedures to be performed for the duration of the study is outlined in tabular form in Appendix 2.The required testing procedures for this protocol are the same as the procedures in Protocol 03-CL-1201.

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

7.1 Clinical Assessments

The following clinical assessments must be appropriately documented in the study eCRF. In addition, any clinical findings that are consistent with an AE must be documented as such in the eCRF (Section 9).

In addition to the clinical assessments outlined below, PIs are to provide continual clinical assessment and monitoring during the active delivery of lucinactant for inhalation. If at any point during the delivery of lucinactant for inhalation, a potential safety risk to the subject is identified, aerosol delivery must be discontinued by activating the ACU 'stop treatment' interface. Any significant clinical findings or observations must be documented and communicated to Discovery at the earliest time point possible.

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 from the time of randomization: 1, 3 (± 15 minutes), 6, 12 (± 1 hour), 18, 24, 36, and 48 hours (± 2 hours) post-randomization.

Subjects randomized to the active study arm will have additional vital signs (respiratory rate and heart rate) documented every 5 minutes (± 2 minutes) during the administration of lucinactant for inhalation for Dosing Group I and II. For Dosing Groups III and IV, vital signs will be documented every 15 minutes (± 5 minutes) after randomization.

For all dosing groups, subjects randomized to the nCPAP only arm will have additional vital signs (respiratory rate and heart rate) documented 15 minutes (± 5 minutes) after randomization.

For all randomized subjects, daily vital sign assessments (body temperature, respiratory rate, and heart rate) must be performed at 0800 hours (± 2 hours) from Study Day 3 to the completion of Study Day 7.

Sustained heart rate < 100 bpm for ≥ 20 seconds must be noted as an AE of bradycardia in the study eCRF.

In this study, a sustained apnea event is defined as lasting ≥ 20 seconds and is coincident with at least one of the following: (1) HR < 100 bpm, (2) desaturation (oxygen saturation < 80%), (3) requirement for intermittent positive pressure breaths using inflating pressures above the set CPAP pressure administered manually or mechanically through any patient interface.

7.1.2 Body Weight

The first body weight measurement obtained after randomization must be recorded in the study eCRF. In addition, birth weight will be documented in the study eCRF as part of the birth history.

7.1.3 Pulse Oximetry

SpO_2 will be monitored continuously from the time of randomization until completion of Study Day 7.

Sustained SpO_2 < 80% for ≥ 20 seconds must be recorded as an AE in the study eCRF.

7.1.4 FiO_2

FiO_2 values will be recorded at different times throughout the study. At a minimum, FiO_2 values are: 1) recorded at specified time points while a subject is receiving nCPAP, 2) recorded every 12 hours when a subject is receiving other types of respiratory support or supplemental oxygen, 3) recorded every 15 minutes for 3 hours after randomization, and 4) recorded every 6 hours from randomization through 72 hours.

7.1.5 Monitoring of Carbon Dioxide Levels

PCO_2 measurements for subjects in both the active and control groups will be resulted through the use of continuous transcutaneous monitor.

PCO_2 monitoring must be initiated following randomization (for subjects randomized to the active study arm, monitoring must be initiated at least 30 minutes before the start of ADS

delivery) and continue for 72 hours post randomization. The transcutaneous monitor must be calibrated for accuracy against blood gas values (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.

In the eCRF, PCO_2 values will be recorded every 15 minutes through 3 hours after randomization, and every 6 hours from randomization through 72 hours.

7.1.6 Physical Examination

A complete physical examination will be performed by either the PI or designee. The designee may be a qualified member of the site-based study staff (such as a nurse practitioner, NICU nurse, or physician assistant); physical examinations performed at screening must be reviewed and approved by the PI. Any new 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).

7.1.8 Chest Radiograph

A chest radiograph for the diagnosis of RDS will be performed as part of the screening assessment.

A chest radiograph will also be required during the first 7 study days for study subjects who meet 1 or both of the following: (1) non-emergent intubation for any indication (in such instances, all efforts must be made to obtain the chest radiograph prior to intubation, if the procedure does not delay or compromise the care of the subject); or, (2) worsening of respiratory status in accordance to Section 7.5.

7.1.9 Gastric Liquid Volume

Gastric liquid volume will be assessed 30 minutes (± 15 minutes) following completion of lucinactant for inhalation administration. Enteral feedings are to be held during administration and for at least 1 hour following completion of lucinactant for inhalation administration.

7.1.10 Defecation

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

7.2 Medical Information

Relevant medical information, including maternal-birth history, pertinent respiratory history, medical history (from birth to randomization) and information regarding underlying diseases will be recorded at screening.

7.3 Concomitant Medications

Concomitant medications required for the general care of the subject are permitted, with the exception of investigational agents and investigational medical devices.

All concomitant medication and concurrent therapies will be documented from birth until the time the subject completes the study (36 weeks PMA or discharge) or withdraws (Section 10.2). Dose, route, unit, frequency of administration, indication for administration, and dates of medication will be captured.

7.3.1 Use of Additional Surfactant Replacement Therapies

Following lucinactant for inhalation administration, commercially available SRTs consistent with the current standard of care may be administered only in circumstances where it is in the best interest of subject's safety, and in the PI's best medical judgment.

Subjects receiving commercially available SRT during study participation will be considered treatment failures, and as such, will continue to be followed for safety follow-up until study completion.

The study criteria for worsening of respiratory status are outlined in Section 7.5.

7.4 Demographics

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

7.5 Worsening Respiratory Status

Subjects meeting the criteria of worsening respiratory status (outlined within this section) 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).

Refer to Section 7.1.8 for required chest radiograph.

7.5.1 Worsening Respiratory Status Criteria

A subject will be categorized as having worsening respiratory status if they meet at least 1 of the following criteria:

1. The need for additional surfactant therapy following exposure to lucinactant for inhalation
2. A sustained $FiO_2 > 0.50$ for > 30 minutes to maintain an $SpO_2 > 90\%$
3. A $PCO_2 > 65$ mm Hg on ≥ 2 consecutive occasions
4. Persistent, arterial pH < 7.20 (if blood gas values are available and obtained for non-study related clinical assessment)
5. Any sustained apneic event defined as ≥ 20 seconds and meeting at least one of the following: (a) HR < 100 bpm, (b) desaturation (oxygen saturation < 80%), (c) requirement for intermittent positive pressure breaths using inflating pressures above the set CPAP pressure administered manually or mechanically through any patient interface
6. Intubation for any reason (except for elective surgical procedures)
7. nCPAP > 7 cm H_2O
8. Initiation of intermittent positive pressure breaths using inflating pressures above the set CPAP pressure administered manually or mechanically through any patient interface
9. Death while on study
10. The study PI determines that the subject has worsening respiratory status based on their best clinical judgment.

7.5.2 Worsening Respiratory Status Categories

Worsening respiratory status will be categorized as follows:

- Early worsening : worsening respiratory status occurring ≤ 72 hours after birth
- Late worsening: worsening respiratory status occurring > 72 hours and ≤ 7 days after birth

7.6 Respiratory Support and Oxygen Delivery

Study subjects must be maintained on nCPAP from the time of randomization until they have completed delivery of lucinactant for inhalation as outlined in Section 5.4. The management of respiratory support (to include nCPAP) and oxygen delivery after the completion of lucinactant for inhalation delivery will be at the discretion of the study PI.

During nCPAP delivery subjects must be closely monitored for complications related to placement of the patient interface (eg, bi-nasal prongs). Assessment must include but not be limited to evaluation for the following conditions: bleeding, apparent obstruction of the nares, occlusion of interface requiring removal and replacement, nasal irritation (erythema of nares or septum, inflammation of nares or septum). Evidence of these conditions should be reported as an AE and treated in accordance with local institutional practice.

FiO_2 values (regardless of mode of delivery) will be recorded following randomization and will continue for 72 hours post randomization.

7.6.1 Emergent Respiratory Support

Emergent endotracheal intubation and mechanical ventilation, in accordance with local institutional guidance, must be initiated at any time if deemed necessary for subject safety. In such instances, the subject must be evaluated for worsening of respiratory status (Section 7.5.2).

Any clinical event indicating a need for mechanical ventilation, additional pressure 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.

7.6.2 Documentation During Primary and Extended Observation Period

From the time of randomization until completion of Study Day 7 the following must be evaluated and documented in the study eCRF:

1. Mechanical ventilation: date and time of initiation and discontinuation, the mode, mean airway pressure, respiratory rate, set tidal volume (if appropriate), and FiO_2
    - To be documented every 12 hours (± 1 hour) until mechanical ventilation has been discontinued for > 24 hours
2. Pressure support (to include nCPAP): date and time of initiation and discontinuation, PIP, respiratory rate, CPAP, flow rate, and FiO_2, as appropriate.
    - Primary Observation Period: document at 1, 3 (± 15 minutes), 6, 12 (± 1 hour), 18, 24, 36, and 48 hours (± 2 hours) post-randomization
    - Extended Observation Period: document every 12 hours (± 1 hour) until nCPAP has been discontinued for > 24 hours
3. Supplemental oxygen (FiO_2 > 21%): date and time of initiation and discontinuation, mode of delivery (eg, nasal cannula, oxygen hood), and FiO_2, as appropriate.

- After the administration of lucinactant for inhalation, FiO_2 must be documented every 12 hours (± 1 hour) until supplemental oxygen has been discontinued for > 24 hours

4. Intubation: the date and time of intubation for any reason must be documented.

If respiratory support or oxygen delivery is reinitiated following discontinuation, then parameters must again be captured every 12 hours until discontinuation.

7.6.3 Documentation During Final Observation Period

From Study Day 8 until the subject completes or withdraws from the study, the following must be evaluated and documented in the study eCRF:

- Intubation and mechanical ventilation: date and time of initiation and discontinuation
- Pressure support (to include nCPAP): date and time of initiation and discontinuation
- Supplemental oxygen: date and time of initiation and discontinuation, mode of delivery and FiO_2
- Intubation: the date and time of intubation for any reason

7.7 Criteria for Acute Respiratory Deterioration

Subjects must be closely monitored for signs and symptoms of acute respiratory deterioration throughout the study period. Any clinical signs of acute respiratory deterioration must be treated in accordance with local institutional practices and under the best medical judgment of the study PI.

Acute respiratory deterioration must be reported as an AE and, for study purposes, is defined by an increased respiratory rate or an observed increase in respiratory effort (work of breathing) plus at least one of the following criteria:

1. An $FiO_2 \geq 0.70$ or a sustained increase from baseline by ≥ 0.30 to maintain oxyhemoglobin saturation
2. A $PCO_2 > 70$ mm Hg or a progressive increase from baseline to ≥ 20 mm Hg above baseline and confirmed with a blood gas
3. Recurring episodes of bradycardia defined as a heart rate < 100 bpm for ≥ 20 seconds
4. A sustained apnea event, defined as apnea for at least 20 seconds in duration and meeting at least one of the following: (1) HR < 100 bpm, (2) desaturation (oxygen saturation < 80%), (3) requirement for intermittent positive pressure breaths using inflating pressures

above the set CPAP pressure administered manually or mechanically through any patient interface

5. Endotracheal intubation for any reason (with the exception of elective surgical procedures)
6. Initiation of intermittent positive pressure breaths using inflating pressures above the set CPAP pressure administered manually or mechanically through any patient interface
7. nCPAP > 7 cm H_2O
8. Death while on study
9. The study PI determines that the subject has worsening respiratory status based on their best clinical judgment (Note: When medical judgment is the sole criteria for stopping therapy, a detailed narrative describing the clinical events and observations supporting the decision to stop therapy needs to be documented.)

8 EVALUATIONS BY VISIT

All of the following assessments will be performed until the time the subject completes the study (36 weeks PMA) or withdraws (Section 10.2).

A Schedule of Events representing the required testing procedures and the associated timeframe to be performed for the duration of the study is outlined in Appendix 2.

8.1 Screening Period

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

- A signed ICF
- Maternal history, to include (Section 7.2):
    a) Rupture of membranes (time relative to birth, type)
    b) Chorioamnionitis (clinical)
    c) Antenatal steroids (number of doses, time relative to birth)
- Birth history, to include (Section 7.2):
    a) Date and time of birth
    b) Mode of delivery (vaginal, C-section)
    c) Single or multiple birth (number)
    d) Apgar score (assessed at 1 and 5 minutes)
    e) Congenital anomaly
- Medical History (Section 7.2)
- Demographics, to include Section 7.4:
    a) Sex
    b) Race
    c) Ethnic origin
    d) Birth weight (grams) (Section 7.1.2)
    e) Gestational age (weeks)
- Initial physical examination findings (Section 7.1.6)
- Inclusion and exclusion criteria (Sections 4.2 and 4.3)
- Chest radiograph (Section 7.1.8)
- Date and time of initial nCPAP or other type of controlled positive pressure ventilation

8.2 Primary Observation Period

The following will be documented for each randomized subject during the Primary Observation Period of the study (≤ 48 hours after randomization [T_0]):

1. Date and time (T_0) of randomization and the study dosing group assignment (Section 5.2.2)
2. The date and time of the initiation and completion of aerosol delivery (Section 5)
3. All AEs, including ADEs (Section 9)

   Peri-dosing events (defined as an AE with an onset time ≤ 2 hours from the time of initiating administration of lucinactant for inhalation) may include but not be limited to:

   - Bradycardia (as noted by HR < 100 bpm for ≥ 20 seconds) (Section 7.1.1)
   - Desaturation (as noted by O_2 saturation < 80% for ≥ 20 seconds) (Section 7.1.3)
   - Gagging/regurgitation
   - Apnea (central, obstructive, or combined) (Section 7.1.1)
   - Pallor
   - Complications related to placement of bi-nasal prongs (bleeding, apparent obstruction of the nares, bi-nasal prongs occlusion requiring removal and replacement, nasal irritation).
4. Respiratory support and supplemental oxygen as outlined in Section 7.6
5. nCPAP settings (Section 5.4), (Section 7.6)
6. FiO_2 values (Section 7.1.4)
7. Signs and symptoms consistent with worsening of respiratory status (Section 7.5)
8. Vital signs and SpO_2 (Section 7.1.1, Section 7.1.3)
9. PCO_2 values (Section 7.1.5)
10. Chest radiograph, as applicable (Section 7.1.8)
11. Gastric liquid volume (Section 7.1.9)
12. Serum electrolytes (Section 7.1.7)
13. Defecation (initial 24 hours following radomization) (Section 7.1.10)
14. Concomitant medications (Section 7.3)
15. Technical performance of the device (Section 5.1.4)
16. The use of pacifiers

8.3 Extended Observation Period:

The following assessments are to be performed during the Extended Observation Period of the study (> 48 hours to ≤ 7 days after date of randomization). Daily measurements are to be obtained as close to 0800 as possible.

1. Assessment and documentation of respiratory support and supplemental oxygen (Section 7.6)
2. Signs and symptoms consistent with worsening of respiratory status (Section 7.5)
3. Vital signs (Section 7.1.1)
4. SpO_2 (Section 7.1.3)
5. Chest radiograph, as applicable (Section 7.1.8)
6. Incidence of AEs, including ADEs (Section 9)
7. Concomitant medications (Section 7.3)

8.4 Final Visit

The Final Visit (36 weeks PMA or discharge, whichever comes first) will include the following:

1. Documentation of respiratory support and supplemental oxygen (Section 7.6)
2. AEs, including ADEs (Section 9)
3. Physical examination (including changes from baseline exam) (Section 7.1.6)
4. Occurrence or presence of the following (as applicable):
    a) IVH (worst grade during hospitalization)
    b) Cystic PVL during hospitalization
    c) PDA and related treatments (surgery or pharmacologics)
    d) NEC (stage and related treatments)
    e) Lung air leaks
    f) Pulmonary hemorrhage
    g) Acquired sepsis
    h) Apnea
5. Incidence of BPD
6. The incidence of ROP (Appendix 5) (document onset and severity throughout study participation)
7. Survival (date, time, and cause of death if applicable)

8. Date and time of transfer or discharge from the current hospital (if applicable)
9. Concomitant medications (Section 7.3)

9 ADVERSE EVENT REPORTING

Information regarding the occurrence of AEs, including ADEs, will be assessed from the time of randomization until completion of Final Study Visit.

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

1. Bradycardia: defined as a heart rate < 100 bpm for ≥ 20 seconds
2. Desaturation: defined as SpO_2 < 80% for ≥ 20 seconds
3. A sustained apnea event defined as lasting ≥ 20 seconds and is coincident with at least one of the following: (1) HR < 100 bpm, (2) desaturation (oxygen saturation < 80%), (3) requirement for intermittent positive pressure breaths using inflating pressures above the set CPAP pressure administered manually or mechanically through any patient interface.
4. Air leak, including pneumothorax and pneumomediastinum.

Complications related to placement of bi-nasal prongs 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)

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.

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) by telephone, regardless of the relationship (or lack thereof) of the SAE to study participation.

SAEs should be reported to Discovery's reporting line (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 to Discovery at 888-527-9512 (USA).

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 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:

- 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 Medical Monitoring

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

FOR MEDICAL QUESTIONS, PLEASE CONTACT THE MEDICAL MONITOR:

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

or,

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

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

Reporting Line (24/7/365): (855) 4ACTADS (422-8237) (USA)
Fax Number: (888) 527-9512 (USA)

FOR ADDITIONAL ASSISTANCE, PLEASE CONTACT YOUR CRA OR:

Christine E. Buben (Director, Clinical Operations, Discovery)
Office: (215) 488-9479
Cell: (215) 527-5618
email: CBuben@DiscoveryLabs.com

10 DISCONTINUATION AND REPLACEMENT OF SUBJECTS

10.1 Early Discontinuation of Lucinactant for Inhalation

The PI or the subject's legal guardian may discontinue the administration of lucinactant for inhalation at any time point before or during the administration of lucinactant for inhalation. Discontinuation may be based on but not limited to the criteria outlined in Section 5.1.2.

1. Device failure or malfunction, including error codes or treatment interruptions
2. Pulmonary hemorrhage or other AE/ADE
3. In the PI's best medical judgment, initiating or continuing the subject's exposure to lucinactant for inhalation is not in the best interest of the subject's safety.
4. Signs of respiratory deterioration as evidenced by an increased respiratory rate or an observed increase in respiratory effort (work of breathing) plus at least one of the following: an $FiO_2 \geq 0.70$ or a sustained increase from baseline by ≥ 0.30 to maintain oxyhemoglobin saturation; a $PCO_2 > 70$ mm Hg or a progressive increase in PCO_2 from baseline to ≥ 20 mm Hg above baseline and confirmed with a blood gas; recurring episodes of bradycardia defined as a heart rate of < 100 bpm for ≥ 20 seconds; a sustained apneic event, defined as apnea at least 20 seconds in duration and meeting at least one of the following: (1) HR < 100 bpm, (2) desaturation (oxygen saturation < 80%), (3) requirement for IPP breaths using inflating pressures above the set CPAP pressure administered manually or mechanically through any patient interface.

10.2 Study Withdrawal

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

If, at the end of the Final Study Period, 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 following exposure to study aerosol, the subject will be considered lost to follow-up.

10.3 Early Study Termination

The study may be terminated prematurely due to safety reasons by the SRC (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, 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 SRC in order to adequately assess safety in the dose group.

11 PROTOCOL VIOLATIONS

A protocol violation occurs when the subject or 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.

When a protocol violation occurs, it will be discussed with the PI. All protocol violations 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

The protocol, including any amendments and the ICF, will be submitted to an IRB at each investigational site for approval to conduct the study. Before the initiation of the study at each investigational site, a designee at the site will forward to Discovery a copy of the site's local IRB approval to conduct study 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 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 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 for approval and subsequent implementation at the study site. Protocol modifications (ie, amendments) may only be enacted by Discovery.

The IRB 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)
2. Any new study information that may adversely affect subject safety or study conduct
3. Annual study updates or IRB requests for reassessment of the study
4. Timely communication of significant actions and related findings from the SRC (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 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, and local regulations.

The PI will prepare the ICF and HIPAA authorization 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. The ICF generated by the PI must be acceptable to Discovery and be approved by the IRB. The PI will send an IRB-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 consent of a subject's legally authorized guardian, using the IRB-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.

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 approximately 64 subjects will be enrolled into the study with approximately 32 subjects randomized to the active surfactant arm. The sample size is based on the number of subjects necessary to evaluate the safety and tolerance of lucinactant for inhalation.

Sample size calculations to demonstrate clinical effect will not be performed as efficacy is an exploratory objective.

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

13.1 Statistical and Analytical Plans

The statistical analysis will be based on all randomized subjects in the study, ie, the Intent-to-Treat (ITT) population. In addition, all evaluable subjects will be analyzed for efficacy signals. Evaluable subjects are those in whom complications of prematurity (eg, PDA, IVH, sepsis,) do not preclude assessment of efficacy signals (eg, improvement in oxygenation, need for intubation and IMV). For all variables, summary statistics will be provided by dosing group, including frequency count and percentage for discrete or categorical variables, and mean, standard deviation, median, minimum, and maximum for continuous variables. In addition, time-to-event variables will be summarized using Kaplan-Meier methodology. Incidence and rates of death, BPD, survival without BPD, and worst-stage ROP at 36 weeks PMA will be summarized.

If no values are recorded in a given eCRF data field, they will be treated as missing and will not be imputed.

13.2 Interim Analyses

The SRC will evaluate the tolerability and safety data upon completion of 72 hours for active subjects, and all available safety endpoint data for control subjects (Section 6). An independent statistician, not a member of the committee, will be responsible for the statistical analysis of the data to be reviewed at each meeting. The committee will review the AEs related to dosing (Appendix 1) and all AEs and device effects. The SRC will have the authority to recommend suspending enrollment or not based on their independent review findings relevant to the safety of study subjects. At each review, the control subjects will be summarized in aggregate.

13.3 Sample Size and Randomization

Sample size is not based on statistical estimation for this phase 2 study. The number of subjects randomized (approximately 8 in each active group and approximately 8 in each control group) will be considered sufficient to establish safety and tolerability before proceeding to the next higher dose. The total of approximately 32 subjects assigned to the active arm and approximately 32 subjects for the control arm for the entire study is considered sufficient to assess overall safety and tolerability.

14 DATA COLLECTION, RETENTION AND MONITORING

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

Before site initiation, all participating PIs must agree to permit study-related monitoring, audits, IRB/IEC reviews, as well as access and review of source data by 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, except as necessary for monitoring by the FDA. The investigators must also comply with all applicable privacy regulations (eg, HIPPA, EU Data Protection Directive 95/46/EC).

Additional subject confidentiality issues (if applicable) are covered in the Clinical Study Agreement (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 treated with lucinactant for inhalation.

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

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, the following will be observed:

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

communications to Discovery of all IRB/IEC communications (to include reviews and subsequent actions) concerning the study.

- The clinical site monitor(s) will perform periodic visits to each clinical site during the course of the study to ensure the study protocol is being followed and that:
    a) Drug and device inventories are being properly maintained and documentation of vial usage is accurate and complete.
    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.
- 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 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 IRBs are 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 (see Appendix 6), 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. Ensure that the requirements relating to obtaining informed consent and IRB review and approval meet federal guidelines, as stated in 21 CFR 50 and 21 CFR 56.
4. Report any AEs/SAEs that occur in the course of the study to Discovery or designee, in accordance with 21 CFR 312.64.
5. Ensure that all associates, colleagues, and employees assisting in the conduct of the study are informed about their obligations in meeting the above commitments.
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.
8. Ensure the local IRB complies with the requirements of 21 CFR 56 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 and Discovery or designee all changes in the research activity and all unanticipated problems involving risks to subjects or others (to include amendments and IND safety reports).
10. Seek IRB 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.

16 REFERENCES

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Appendix 1 Protocol Definitions

Definitions	
Aerosol, study	Output of ADS device (eg, aerosolized lucinactant)
Aerosol, time	Length of time subject is exposed to aerosolized lucinactant
AEs related to dosing	1. Bradycardia: heart rate < 100 bpm for ≥ 20 seconds 2. Desaturation: SpO_2 < 80% for ≥ 20seconds 3. Apnea: for purposes of this study a sustained apnea event is defined as lasting ≥ 20 seconds and is coincident with at least one of the following: (1) HR < 100 bpm, (2) desaturation (oxygen saturation < 80%), (3) requirement for intermittent positive pressure breaths using inflating pressures above the set CPAP pressure administered manually or mechanically through any patient interface 4. Complications related to placement of bi-nasal prongs: a) bleeding b) apparent obstruction of the nares c) occlusion of the interface requiring removal and replacement d) nasal irritation (erythema of nares or septum, inflammation of nares or septum)
Air leak, lung	Chest radiographic evidence of air leak (pneumothorax, pulmonary interstitial emphysema, pneumomediastinum, pneumopericardium, subcutaneous emphysema) resulting from lung parenchymal disease.
Arm, active	The study subpopulation that is determined through randomization to be administered lucinactant for inhalation in addition to nCPAP
Arm, control	The study subpopulation that is determined through randomization to be administered nCPAP alone
Capillary aerosol generator (CAG)	A technology designed to produce high volume, low-velocity aerosolized lucinactant for intra-pulmonary delivery.
Final Visit	The concluding study visit to occur at 36 weeks PMA or at the time of discharge or withdrawal (whichever comes first).
Gestational age	Best obstetrical estimate or ultrasound.

Definitions	
Intraventricular hemorrhage (IVH)	Detected by cranial ultrasound. See Appendix 3.
Lucinactant for inhalation	The active investigational agent, lyophilized lucinactant, in combination with the investigational delivery device, Aerosurf Delivery System
nCPAP settings (recommended as initial settings)	CPAP = 5-6 cm H_2O to obtain appropriate SpO_2, defined as: • $SpO_2 \geq 88\%$ and $\leq 95\%$ • $FiO_2 \geq 0.30$ (based on inclusion criteria met; refer to Section 4.2) and < 0.50
Necrotizing enterocolitis (NEC)	Using the grading scale of Bell, et al. (Appendix 4).
NIPPV	Nasal Intermittent Positive Pressure Ventilation includes all forms of nasal ventilation; bi-level, synchronized, or continuous. NIPPV cannot be used to qualify the infant or be used during aerosol treatment.
Oxygen, off supplemental	Neonates who do not require any form of supplemental oxygen for $\geq$ 24 hours. Neonates requiring oxygen only during feeding are considered off supplemental oxygen.
Oxygen, other delivery modes	Includes all modes of non-pressure support (nasal cannula, oxygen hood, etc.)
Oxygen, supplemental	Any requirement for additional oxygen ($FiO_2 > 0.21$).
Period, extended observational	The study timeframe occurring > 48 hours from randomization until $\leq$ day 7
Period, final observational	The study timeframe occurring > day 7 to $\leq$ 36 weeks PMA
Period, primary observational	The study timeframe occurring $\leq$ 48 hours from randomization
Periventricular leukomalacia (PVL)	The presence of one or more echolucent cysts in and around the cerebral ventricles noted on cranial ultrasounds. This is **not** the early presence of bright echogenic areas (known as "flares" or periventricular "echodensities").
Physical exam	Includes the following organ systems: cardiac, respiratory, abdomen, genitalia and perineum, skin, extremities, head, neck and mouth, and neurological.
Pressure support	Includes all modes of pressure support (IMV/SIMV, AC, HFV, CPAP, etc.)

Definitions	
Pulmonary hemorrhage	The presence of bright red blood in a tracheal aspirate deemed not to be the result of tracheal trauma, associated with deterioration in the subject's condition and a change in chest radiographs.
Study dosing	The randomized to receive 1 dose of lucinactant for inhalation through an investigational ADU device for either 30 or 45 minutes in conjunction with the protocol required nCPAP support.
Worsening of respiratory status	A subject will be categorized as having worsening respiratory status if they meet at least 1 of the following criteria: (1) need for additional surfactant therapy following exposure to lucinactant for inhalation; (2) a sustained $FiO_2 > 0.50$ for > 30 minutes to maintain an oxygen saturation (SpO_2) > 90%; (3) a $PCO_2 > 65$ mm Hg on ≥ 2 consecutive observations; (4) persistent, arterial pH < 7.20 (if blood gas values are available and obtained for non-study related clinical assessment); (5) any sustained apneic event, defined as ≥ 20 seconds and meeting at least one of the following: (a) HR < 100 beats per minute (bpm), (b) desaturation (oxygen saturation < 80%), (c) requirement for intermittent positive pressure breaths using inflating pressures above the set CPAP pressure administered manually or mechanically through any patient interface; (6) intubation for any reason (except for elective surgical procedures); (7) nCPAP > 7 cm H_2O; (8) initiation of intermittent positive pressure breaths using inflating pressures above the set CPAP pressure administered manually or mechanically through any patient interface; (9) death while on study; or (10) the study PI determines the subject to have worsening respiratory status based on their best clinical judgment.
Worsening of respiratory status, early	Worsening occurring ≤ 72 hours after birth
Worsening of respiratory status, late	Worsening occurring > 72 hours and ≤ 7 days after birth

Appendix 2 Protocol Event Schedule Summarization

Measurement/Procedure	Study Period				
	Screening	Primary Observation	Extended Observation	Final Observation	
		Days 1-2	Days 3-7	Day 8 to 36w PMA	Final Visit (36w PMA)
Informed Consent/HIPAA	X				
Inclusion/Exclusion Criteria	X				
Demographics	X				
Maternal/Birth History[1]	X				
Physical Exam	X				X
Chest Radiograph[2]	X				
Randomization		X			
Lucinactant for inhalation		X			
Body Weight		X[1]			
Defecation[3]		X			
Vital Signs		X[4]	X[4]		
Monitoring of SpO_2 [5]		X	X		
Monitoring of PCO_2[6]		X			
Respiratory support and O_2 delivery	X	X	X	X[7]	X[7]
Serum Electrolytes		X[8]			
Gastric Liquid Volume[9]		X			
Peri-Dosing Events[10]		X			
Adverse Events		X	X	X	X
Adverse device effects		X			
Concomitant Medication		X	X	X	X

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

1 Birth weight will be captured with birth history and as the first body weight obtained after randomization (Section 7.1.2).

2 A chest radiograph prior to intubation (refer to Sections 7.1.8, 7.5), is required if such a procedure does not delay or compromise the emergent care of the subject.

3 The number of stools occurring within 24 hours from the time of randomization is to be recorded (Section 7.1.10).

4 Vital signs will be documented within 15 minutes (± 5 minutes) prior to randomization. For the active arms, vital signs will be documented every 5 minutes (± 2 minutes) during dosing for Dosing Group I and II; every 15 minutes (± 5 minutes) during dosing for Dosing Group III and IV. For the control arms, vital signs will be documented at 15 minutes (± 5 minutes) post randomization (Section 7.1.1). In addition, record at 1, 3 (± 15 minutes), 6, 12 (± 1 hour), 18, 24, 36 and 48 hours (± 2 hours) post randomization and daily at 0800 (± 2 hours) on days 3 to 7 for all randomized subjects.

5 Continuous monitoring of oxygen saturations by pulse oximetry will be initiated at the time of randomization and continued until completion of Study Day 7 (Section 7.1.3).

6 Continuous trancutaneous PCO_2 monitoring is to be initiated following randomization and at least 30 minutes prior to the start of ADS delivery, and continued for 72 hours post randomization (Section 7.1.5).

7 Only the date and time of the initiation and discontinuation of ventilator and pressure support is to be documented in the study eCRF from Study Day 8 to Final Study Visit (Section 7.6).

[8] Serum electrolytes are to be evaluated 24 hours from randomization (± 6 hours) (Section 7.1.7)

[9] Gastric liquid volume will be assessed 30 minutes (± 15 minutes) following completion of lucinactant for inhalation administration. Enteral feedings are to be held during and ≥ 1 hour following completion of lucinactant for inhalation administration (Section 7.1.9).

[10] Peri-dosing events are defined as any adverse event with an onset time ≤ 2 hours from the time of initiating administration of lucinactant for inhalation

Appendix 3 Papile Scoring System for Intraventricular Hemorrhage (IVH)

Any method of classifying IVH must describe the location of the hemorrhage and the size of the ventricles. Numerous systems have been proposed, but the one developed by Papile is most often used. Although it was developed for CT scanning, it has also been applied to ultrasonography.

Grade I. Subependymal, germinal matrix hemorrhage.

Grade II. Intraventricular hemorrhage without ventricular dilatation.

Grade III. Intraventricular hemorrhage with ventricular dilatation.

Grade IV. Intraventricular hemorrhage with parenchymal extension.

Gomella, TL *et al.* Neonatology: Management, Procedures, On-Call Problems, Diseases and Drugs, Appleton & Langes, 1994, p.386.

Appendix 4 Scoring System of Bell for Necrotizing Enterocolitis (NEC)

The presentation may vary from a benign gastrointestinal abnormality such as abdominal distention (the most frequent early sign, noted in 70% of cases), ileus, and increased volume of gastric aspirate or bilious aspirate (two-thirds of cases) to frank signs of shock, blood per rectum, peritonitis, and perforation. It can also present with nonspecific signs such as labile temperature, apnea, bradycardia, or other signs that would make one suspect sepsis. The clinical syndrome has been classified into stages by Bell et al (1978) and modified by Walsh and Kliegman (1986) to include systemic, intestinal, and radiographic findings.

A.Stage I: Suspected NEC

1.Systemic findings are nonspecific, including apnea, bradycardia, lethargy, and temperature instability.
2.Intestinal findings include gastric residuals and guiac-positive stools.
3.Radiographic findings are normal or nonspecific.

B.Stage IIA: Mild NEC

1.Systemic findings are similar to Stage 1.
2.Intestinal findings include prominent-abdominal distention with or without tenderness, absent bowel sounds, and gross blood in the stools.
3.Radiographic findings include ileus, with dilated loops with focal areas of pneumatosis intestinalis.

C.Stage IIB: Moderate NEC

1.Systemic findings include mild acidosis and thrombocytopenia.
2.Intestinal findings include abdominal wall edema, tenderness with or without a palpable mass.
3.Radiographic findings include extensive pneumatosis and early ascites. Intrahepatic portal venous gas may be present.

D.Stage IIIA: Advanced NEC

1.Systemic findings include respiratory and metabolic acidosis, assisted ventilation for apnea, decreasing blood pressure and urine output, neutropenia, and disseminated intravascular coagulation (DIC).
2.Intestinal findings include spreading edema, erythema, and induration of the abdomen.

3.Radiographic findings include prominent ascites and possibly persistent sentinel loops with no perforation.

E.Stage IIIB: Advanced NEC

1.Systemic findings reveal deteriorating vital signs and laboratory indices, shock syndrome, and electrolyte imbalance.

2.Intestinal and radiographic findings reveal evidence of perforation.

Gomella, TL, et al. Neonatology: Management, Procedures, On-Call Problems, Diseases and Drugs, Appleton & Langes, 1994, p.379.

Appendix 5 International Classification of Retinopathy of Prematurity (ROP)

The International Classification of ROP is a general agreement on staging of active disease.

Stage I.	A thin demarcation line develops between the vascularized region of the retina and the avascular zone.
Stage II.	This line develops into a ridge protruding into the vitreous, in which there is histologic evidence for an arteriovenous shunt.
Stage III.	Extraretinal fibrovascular proliferation occurs with the ridge. Neovascular tufts may be found just posterior to the ridge.
Stage IV.	Fibrosis and scarring occur as the neovascularization extends into the vitreous. Traction occurs on the retina, resulting in retinal detachment.
Plus disease	Noted when vessels posterior to the ridge become dilated and tortuous (eg, stage III+)

Gomella, TL, et al. Neonatology: Management, Procedures, On-Call Problems, Diseases and Drugs, Appleton & Langes, 1994, p.438.

Appendix 6 Investigator Agreement Form

Study Title: A Multicenter, Randomized, Open-Label, Controlled Trial to Assess the Safety and Tolerability of Lucinactant for Inhalation in Preterm Neonates 26 to 28 Weeks PMA

Study Number: 03-CL-1401

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

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: _____