WINDTREE THERAPEUTICS, INC.

Statistical Analysis Plan

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

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Statistical Analysis Plan

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By signing below, I have read through the entire statistical analysis plan and agree to implement the plan.

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EXECUTIVE SUMMARY

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

This is a multinational, multicenter, randomized, double-blind (masked), controlled study in 26 to 32 completed weeks PMA preterm infants. Infants will be randomized into 1 of 2 parallel treatment groups, with 3 repeat doses allowed if repeat dose criteria are met. Reconstituted lyophilized lucinactant (reconstituted with sterile water for injection) will be aerosolized by the investigational device, the Aerosol Delivery System (ADS), using the capillary aerosol generator and introduced into the nCPAP circuit. Those infants randomized to the control arm will receive nCPAP alone.

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. 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: 1) the aerosol concentration, 2) the minute ventilation of the infant, and 3) the administration time of the aerosol.

The first 2 infants enrolled at each site will receive open-label active treatment (lucinactant for inhalation); all subsequent infants will be randomized into the two masked treatment groups.

Treatment Group	Study Assignment
Lucinactant	Lucinactant for inhalation 160 mg TPL/kg (administered over 100 minutes) in conjunction with nCPAP (n = up to 35) Up to 3 repeat doses of 80 mg TPL/kg are to be given if repeat dosing criteria are met.
Control	nCPAP alone (sham treatment) for 110 minutes (n = up to 35) Up to 3 repeat sham treatments of 50 minutes are to be given if repeat dosing criteria are met.

Note: Masking procedures will be followed for all doses (initial and repeat).

Due to business considerations (and not as a result of safety concerns), enrollment for the study was terminated early on December 10, 2020. The last subject was enrolled on 27 November, 2020

and the last visit is expected on 19 January, 2021. A total of 12 subjects were enrolled. As a result, the planned analyses will be significantly curtailed and no statistical testing will be performed.

The independent data monitoring committee (DMC) was to evaluate the degree of risk involved in study participation and oversee the safety and welfare of study subjects. During the primary phase (all subjects have not yet completed 36 weeks PMA), the chair received regular reports on SAEs and AEs. The DMC was to have conducted 1 preplanned meeting after approximately 33% of subjects have been enrolled, which was cancelled.

Repeat dosing will be allowed up to 36 hours following randomization. Subjects meeting the repeat dosing criterion will receive up to 3 additional treatments of either 80 mg TPL/kg or sham treatment. The control subjects that meet the repeat dosing criteria must carry out all the procedures conducted for the active subjects to protect study blinding.

The repeat treatment criteria are defined as: 1) At least 20 minutes from completion of the previous treatment, and 2) Subject has a need for fraction of inspired oxygen (FiO_2) > 0.21 to maintain oxygen saturation as measured by pulse oximetry (SpO_2) of 90% to 95%. The repeat treatment should occur as soon as possible after the 20-minute time period has elapsed, but no more than 1 hour after meeting criteria.

Primary Study Period:

For the primary study period (enrollment to 36 weeks PMA), subjects will be followed for safety and efficacy evaluations until the subject is 36 weeks PMA, is discharged, is transferred, or has died. Descriptive statistics (number of subjects, percent, mean, standard deviation, median, minimum, maximum) will be presented by treatment group, defined the active dose (n = 35) and the nCPAP only (sham treatment) (n = 35). A final visit will occur at 36 weeks PMA or at the time of discharge or transfer (whichever occurs first) for all subjects.

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

Secondary endpoints of this study include:

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

6. All-cause mortality through 28 days of life and 36 weeks PMA
7. Common complications of prematurity through 36 weeks PMA
8. Duration of MV and oxygen requirement through 36 weeks PMA
9. Changes in fraction of FiO_2, partial pressure of carbon dioxide (PCO_2), and SpO_2 over the first 72 hours of life, and over the first 7 days of life for FiO_2

Safety endpoints in the study include:

1. All-cause mortality through 28 days of life (date and time of death, if applicable)
2. AEs, including adverse device effects (ADEs) and AEs of special interest including AEs during the dosing period, complications related to placement of bi-nasal prongs, and air leak. AEs that are ongoing at 36 weeks PMA will be followed for an additional 30 days
3. Concomitant medications
4. Use of respiratory support and supplemental O_2, including the need for endotracheal intubation and MV and the mode of respiratory support, including oxygen only (without positive pressure)
5. Physical examinations
6. Assessments of vital signs, O_2 saturation, and chest radiography prior to intubation
7. Monitoring of PCO_2 and FiO_2

Follow-Up Period:

Due to the early termination of the study, assessments and analysis during the follow-up period were cancelled.

Analysis Populations:

The statistical analysis of both the primary and secondary objectives will be based on all enrolled preterm neonates. Due to the early termination of the study, all enrolled neonates that received any medication will be the only population analyzed. Since all randomizaed subjects received study treatment, this will be described as the ITT population for efficacy analyses and as the safety population for safety analyses; however, the populations will be the same.

For all efficacy assessments, only summary statistics without statistical testing will be utilized.

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

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ABBREVIATIONS

Abbreviation	Description
ADE	Adverse device effect
ADS	Aerosurf® Delivery System
AE	Adverse event
BPD	Bronchopulmonary dysplasia
CAG	Capillary aerosol generator
Cl/Cl^-	Chloride/Chloride ion
DMC	Data monitoring committee
FiO_2	Fraction of inspired oxygen
IMV	Intermittent mechanical ventilation
IP	Investigational product
ITT	Intent-to-treat
IVH	Intraventricular hemorrhage
IWRS	Interactive web-response system
K/K^+	Potassium/Potassium ion
LS	Least squares
MAP	Mean airway pressure
MedDRA	Medical Dictionary for Regulatory Activities
MMAD	Mass median aerodynamic diameter
MV	Mechanical ventilation
Na/Na^+	Sodium/Sodium Ion
nCPAP	Nasal continuous positive airway pressure
NEC	Necrotizing enterocolitis
NICU	Neonatal intensive care unit
PCO_2	Arterial carbon dioxide
PDA	Patent ductus arteriosus
PMA	Post-menstrual age
PVL	Periventricular leukomalacia
RDS	Respiratory distress syndrome
ROP	Retinopathy of prematurity
SAE	Serious adverse event
SpO_2	Oxygen saturation as measured by pulse oximetry
SAP	Statistical analysis plan
SOC	System Organ Class
SRC	Safety Review Committee
TEAE	Treatment-emergent adverse event
TPL	Total phospholipids
UADE	Unanticipated adverse device effect
WHO	World Health Organization

1 OVERVIEW

This statistical analysis plan (SAP) provides a comprehensive and detailed description of strategy, rationale, and statistical techniques to be used to assess safety and efficacy in the 03-CL-1702 study of lucinactant for inhalation in preterm neonates. The purpose of the SAP is to ensure the credibility of the study findings by pre-specifying the statistical approaches to the analysis of study data prior to database lock. This SAP provides additional details concerning the statistical analyses that are outlined in the protocol.

Note: this study was terminated early due to business considerations and not as a result of any safety concern. As a result, only 12 subjects were enrolled. Thus, no statistics will be calculated in this study; only summary statistics will be computed and assessed.

1.1 Background

1.1.1 Treatment of Neonatal Respiratory Distress Syndrome

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

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

In order to avoid endotracheal intubation and MV in preterm neonates with mild-to-moderate RDS, a strategy of using nCPAP as an effective means of providing ventilatory support is now accepted

and recommended practice (3,4,5,6,11). nCPAP improves respiratory function in neonates by increasing functional residual capacity, improving lung compliance and dilating upper airway structures, thereby improving gas exchange and reducing work of breathing (11,12). Devices that generate and deliver nCPAP, as well as patient interfaces such as nasal prongs, have been specifically designed, manufactured, and made commercially available for use in neonates.

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

Older gestational age infants treated with nCPAP may be at higher risk of air leak than younger infants (21). In a cohort of 297 neonates 25-32 weeks gestation with RDS initially treated with nCPAP alone, 65 (22%) overall required intubation ("nCPAP failure"). The rate of nCPAP failure was 45% in the subgroup 25-28 weeks' gestation, consistent with prior reports, where only 15% of infants 29-32 weeks' gestation had nCPAP failure. Notably, the rate of pneumothorax prior to intubation was 10% in the younger cohort (also consistent with most prior reports) but was 23% in the older gestational age infants as a whole and 47% in those older infants who failed nCPAP.

1.1.2 Development of Aerosolized Device for Lucinactant Delivery

Windtree Therapeutics, Inc. (Windtree) has developed lucinactant for inhalation, an investigational drug-device combination product, to deliver aerosolized SRT to preterm neonates with RDS who are being supported with nCPAP. Lucinactant for inhalation (AEROSURF®) is comprised of a drug component, lyophilized lucinactant, and a device component, the Aerosol Delivery System (ADS). Lyophilized lucinactant is a lyophilized form of SURFAXIN® (lucinactant) Intratracheal Suspension, an exogenous SRT approved by the U.S. Food and Drug Administration (NDA 021746) (not currently marketed based solely on business considerations and not as the result of

any safety, efficacy, or quality concerns). The ADS device uses novel capillary-based aerosol generator technology to aerosolize reconstituted lucinactant, providing a high-density surfactant aerosol output with an appropriate particle size (2 to 4 microns mass median aerodynamic diameter [MMAD]) for respiration and deposition within the neonatal lung. The ADS may allow aerosolized lucinactant to be deposited in the lungs of preterm neonates in sufficient quantities to affect a therapeutic response analogous to that of endotracheal instillation of surfactant.

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 (22). Nonclinical studies using the CAG technology in preterm lambs have demonstrated that aerosolized lucinactant significantly improved lung mechanics and gas exchange compared with preterm lambs receiving CPAP alone (23). In parallel, pilot clinical studies in neonates with RDS (Study KL4-CPAP-01) (24) as well as in adults with asthma and cystic fibrosis (Study KL4-ASTH-01) have demonstrated that lucinactant aerosolized with commercially available nebulizers appears to be generally well-tolerated. The ADS represents the clinical version of the CAG technology, which is being used in clinical trials, to aerosolize lucinactant. This study will employ the next generation, commercially-equivalent, ADS.

The purpose of this study is to evaluate the safety and efficacy of lucinactant for inhalation used in conjunction with nCPAP, in comparison to nCPAP alone, in preterm neonates 26 to 32 completed weeks PMA with RDS.

1.2 Objectives

This study is designed to investigate the safety and efficacy of lucinactant for inhalation in preterm neonates 26 to 32 completed weeks (ie, $26^{0/7}$ to $32^{6/7}$ weeks) PMA. Efficacy and safety will be based on clinical evaluations. The endpoints specified are similar to those in Protocols 03-CL-1201, 03-CL-1401, and 03-CL-1202 to allow for qualitative comparisons.

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

In addition, this study will evaluate the device performance and the ability to administer up to 3 lucinactant for inhalation repeat treatments. The efficacy estimate will be used to calculate the sample size for future studies.

1.2.1 Efficacy Objective

The primary estimand for this study is the occurrence of intubation for the purpose of mechanical ventilation or surfactant administration in preterm neonates 26 to 32 weeks PMA in the intent-to-treat (ITT) population (all randomized subjects). Intercurrent events include 1) treatment administration interruptions and 2) intubations for reasons other than MV or surfactant administration. Due to the small number of subjects as a result of the termination of the study, and that statistical testing will not be performed, intercurrent events will not be evaluated.

1.2.2 Primary Endpoint

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

Subjects meeting the criteria of respiratory failure due to RDS must continue to be followed for all safety evaluations until the time the subject completes the study or withdraws.

1.2.3 Key Secondary Endpoints

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

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

1.2.4 Other Secondary Endpoints

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

1. Common complications of prematurity through 36 weeks PMA (IVH, periventricular leukomalacia [PVL], pulmonary hemorrhage, apnea, NEC, patent ductus arteriosus [PDA], acquired sepsis, ROP).
2. Duration of MV and oxygen requirement through 36 weeks PMA.
3. Changes in fraction of inspired oxygen (FiO_2), partial pressure of carbon dioxide (PCO_2), and oxygen saturation as measured by pulse oximetry (SpO_2).

4. Number/duration of and reason for re-hospitalization and urgent care visits through 12 months corrected age.
5. Respiratory medications through 12 months corrected age.

1.2.5 Safety Evaluations

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

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

1.3 Hypotheses

Due to the fact that the study was terminated early, hypothesis testing and inferential statistics will not be used.

2 INVESTIGATIONAL PLAN

2.1 Study Population

This study population will be comprised of preterm neonates $26^{0/7}$ to $32^{6/7}$ completed weeks PMA who are receiving care in a NICU and are receiving nCPAP as the primary support modality for RDS. This study will enroll preterm neonates who are candidates for SRT and nCPAP.

Subjects will be enrolled by strata: subjects $26^{0/7}$ to $28^{6/7}$ weeks PMA and subjects $29^{0/7}$ to $32^{6/7}$ weeks PMA. The study population will be randomized in a 1:1 ratio into 1 of 2 treatment groups; however, the first 2 subjects at each site will receive open-label active treatment. Approximately 130 subjects (approximately 65 in the active group and 65 in the control group) were to be enrolled at 1 of approximately 10 study sites in the US, Poland, and China, and it is anticipated that approximately 720 subjects will be screened to meet the enrollment goal (8:1 ratio of screened to enrolled).

However, due to business considerations and not as a result of any safety concerns, study enrollment was terminated on 10 December after 12 subjects had been enrolled in Poland.

2.1.1 Inclusion criteria

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

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

2.1.2 Exclusion Criteria

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

1. A heart rate that cannot be stabilized above 100 bpm within 5 minutes of birth
2. Recurrent episodes of apnea requiring positive pressure ventilation (PPV) administered manually or mechanically through any patient interface
3. A 5-minute Apgar score < 5
4. Major congenital malformation(s) or craniofacial abnormalities that preclude the use of nCPAP, diagnosed antenatally or immediately after birth
5. Clinically significant diseases or conditions other than RDS which could potentially interfere with cardiopulmonary function (eg, congenital heart disease, hydrops fetalis or congenital infection)
6. A known or suspected chromosomal abnormality or syndrome
7. Premature rupture of membranes > 3 weeks
8. Hemodynamic instability requiring vasopressors or steroids for hemodynamic support and/or presumed clinical sepsis
9. A need for intubation and/or invasive MV at any time before enrollment into the study
10. The administration (or plan for administration) of any the following:
    a) Another investigational agent or investigational medical device
    b) Any other surfactant agent
    c) Systemic corticosteroids (other than antenatal steroids)
11. Presence of air leak (pneumothorax, pneumomediastinum, pneumopericardium, subcutaneous emphysema, or definite evidence of PIE) on the baseline chest radiograph, or diagnosed via ultrasound or illumination.

2.2 Study Design and Randomization

This is a multinational, multicenter, randomized, double-blind (masked), controlled study to evaluate the safety and efficacy of lucinactant for inhalation in conjunction with nCPAP compared with nCPAP alone. Preterm neonates 26 to 32 completed weeks PMA who are being cared for in a neonatal intensive care unit (NICU) and who are within the first 8 hours after birth, who had successful implementation of noninvasive respiratory support within 60 minutes of birth, and who are candidates for SRT will be enrolled. The preferred initial mode of noninvasive support is study nCPAP; however, other modes are acceptable if the investigator feels it is safe to switch the subject to study nCPAP following consent and screening. There will be 2 phases in the study, a primary

phase through 36 weeks PMA and a longer-term follow-up phase through 1-year corrected age. Data analyses and presentations will be conducted after each phase.

Infants will be randomized into 1 of 2 parallel treatment groups, active (lucinactant for inhalation 160 mg TPL/kg) or control (nCPAP only), with 3 repeat doses allowed if repeat dose criteria are met. Repeat doses will be allowed no sooner than 20 minutes from completion of the previous dose and all repeat doses must be complete within 36 hours after randomization. Reconstituted lyophilized lucinactant (reconstituted with sterile water for injection) will be aerosolized by the investigational device, the Aerosol Delivery System (ADS), using the capillary aerosol generator and introduced into the nCPAP circuit. Those infants randomized to the control arm will receive nCPAP alone.

2.2.1 Treatment Groups

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

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

Treatment Group	Study Assignment
160 mg/kg	Lucinactant for inhalation 160 mg TPL/kg (administered over 100 minutes) in conjunction with nCPAP (n = up to 35) Up to 3 repeat doses of 80 mg TPL/kg are to be given if repeat dosing criteria are met.
Control	nCPAP alone (sham treatment) for 110 minutes (n = up to 80) Up to 3 repeat sham treatments of 50 minutes are to be given if repeat dosing criteria are met.

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

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

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

2.2.2 Repeat Dosing

Up to 3 repeat doses will be allowed for each treatment group. The repeat doses will consist of 80 mg TPL/kg for the active group and 50 minutes of sham ro the control group and will occur if repeat dosing criteria are met. The repeat dosing criterion is defined as 20 minutes from completion of the previous dose and the subject has a need for $FiO_2 > 0.21$ to maintain SpO_2 of 90% to 95%. The repeat treatment should occur as soon as possible after the 20-minute time period has elapsed, but no more than 1 hour after meeting criteria.

As with the initial dose, the randomization system 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 doses.

If, in the opinion of the PI, repeat dosing would compromise the safety of the subject, repeat dosing will not occur. If a subject qualifies for repeat dosing but does not receive repeat dosing, the reason for this will be documented.

2.2.3 Sample Size Justification

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

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

2.2.4 Study Schedule

Schedule of Activities (SOA)

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

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

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

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

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

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

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

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

[7] If discharge occurs after 36 weeks PMA.

[8] 12-months corrected age only.

3 STUDY SUBJECT CHARACTERISTICS

3.1 Subject Disposition

Subject disposition will be summarized by treatment group using frequency and percent. The number of subjects screened and randomized will be described.

The number of subjects who completed the study or died will be summarized using frequency and percent by treatment group and overall. Reasons for early discontinuation from the study include withdrawal of consent and lost-to-follow up. A subject may withdraw consent (through their legally authorized guardian) at any time without prejudice to further care.

The number of subjects who discontinued treatment early will be summarized using frequency and percent by treatment group and overall. Reasons for early discontinuation of treatment include device failure or malfunction, AE or ADE during dosing, PI's best medical judgment, and respiratory deterioration during dosing.

3.2 Demographics and Baseline Characteristics

3.2.1 Demographics

Continuous variables (eg, gestational age, birth weight) will be summarized using mean, standard deviation (SD), median, minimum, and maximum. Categorical variables (eg, sex, race, ethnicity) will be summarized by treatment group using frequency and percent.

3.2.2 Medical, Birth and Maternal History

The mode of delivery (vaginal, c-section), type of birth (single, multiple), and incidence of congenital anomalies will be summarized by treatment group using frequency and percent. The Apgar score at 1 and 5 minutes and antenatal steroid use will be summarized by treatment group using mean, SD, median, minimum, and maximum.

Incidence of medical history findings, incidence and type of ruptured membranes, incidence of clinical chorioamnionitis, and the incidence and number of doses of antenatal steroids will be summarized by treatment group using frequency and percent.

3.3 Study and Concomitant Medication

3.3.1 Compliance

Percent compliance for this study is not applicable as all subjects will be administered at least one dose by study staff in the NICU. The number of subjects who experienced treatment interruptions for the initial or repeat doses will be summarized by treatment group.

3.3.2 Number of Doses

The number of doses (initial and repeat study treatments) received by subjects and the number of times a subject qualified for a repeat dose will be summarized by treatment group.

3.3.3 Previous and Concomitant Medication

Medications taken since birth and concomitant medications will be coded according to the World Health Organization (WHO) drug dictionary. Medications will be summarized using frequency and percentages for each treatment group by drug category and generic name.

3.4 Protocol Violations/Deviations

A protocol violation occurs when the PI fails to adhere to any significant protocol requirement affecting the inclusion, exclusion, subject safety, and primary endpoint criteria. A protocol deviation is any deviation from the protocol that does not rise to the level of a protocol violation. All protocol violations/deviations will be summarized by treatment group and listed by subject.

4 EFFICACY ANALYSIS

The efficacy objective is to assess the size of the clinical effect of lucinactant for inhalation in comparison to nCPAP alone, as demonstrated by the occurence of and time to respiratory failure due to RDS or all-cause death through 72 hours and 28 days, BPD and related severity at 36 weeks PMA, incidence rate of survival without BPD at 36 weeks PMA, oxygen saturation and use of supplemental oxygen, common complications of prematurity, duration of MV and oxygen requirement, physiologic parameters (FiO_2, PCO_2, and SpO_2), and number/ duration of re-hospitalizationb and urgent care visits. In addition, the study will evaluate the device performance and the ability to administer up to 3 lucinactant for inhalation repeat treatments.

Given that only 12 subjects were enrolled prior to study termination, hypothesis testing will not be done and statistical tests will not be performed.

4.1 Efficacy Populations

For efficacy analyses, subjects will be summarized according to their assigned (randomized) treatment. The subjects enrolled open-label with active treatment (the first 2 subjects from each site) will not be summarized separately.

The analysis of both the primary and secondary objectives will be based on all enrolled preterm neonates (ITT population).

4.2 Statistical Analysis

All analyses will be performed for all subjects combined and by treatment group. Only summary statistics will be used.

All continuous variables (eg, birth weight, body temperature, PCO_2) will be summarized using number (n), mean, standard deviation (SD), median, 1st quartile, 3rd quartile, minimum, and maximum. All discrete variables (eg, sex, AEs, common complications of prematurity), will be summarized using frequency (n) and percent.

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

4.2.1 Primary Efficacy Endpoint

The primary endpoint is the occurrence of respiratory failure due to RDS, defined as the number of subjects who need intubation for surfactant administration and/or intubation (including intratracheal catheter placement) for MV or all-cause death within 28 days of life.

4.2.2 Key Secondary Endpoints

Key secondary endpoints include the occurrence of respiratory failure due to RDS or death within 72 hours; the occurrence of respiratory failure due to RDS (without death) within 72 hours and 28 days of life; and time to respiratory failure due to RDS or death within 72 hours of life and 28 days of life, presented by treatment group.

BPD is defined as the need for supplemental oxygen above room air (21%) at 36 weeks PMA. The number and percent of subjects who develop BPD by 36 weeks PMA will be summarized by treatment group. The number and percent of subjects who are alive and without BPD at 36 weeks PMA will be summarized by treatment group. Furthermore, the severity of BPD, based on NIH

definition, will be assessed. The severity of BPD is defined as, in addition to supplemental oxygen > 21% for at least 28 days, breathing room air (21%) or 22% at 36 weeks PMA or discharge is mild, moderate is > 22% to < 30% oxygen at 36 weeks PMA or discharge, and severe is ≥ 30% oxygen and/or positive pressure at 36 weeks PMA or discharge. The BPD severity will be summarized by treatment group.

4.2.3 Other Secondary Endpoints

For other secondary endpoints include common complications of prematurity, gas exchange parameters (ie, FiO_2, transcutaneous PCO_2, SpO_2), duration of MV and oxygen requirement (the sum of all time periods using MV and supplemental oxygen through 36 weeks PMA, respectively), and duration and number of re-hospitalization and urgent care visits (through 12 months corrected age) will be summarized by treatment group. The reason for re-hospitalization and urgent care visits and repiratory medications (through 12 months corrected age) will be listed.

Common complications of prematurity through 36 weeks PMA (apnea, air leak, IVH, PVL, pulmonary hemorrhage, NEC, PDA, acquired sepsis, and ROP) will be summarized by treatment group using frequency and percent by treatment group.

Change in FiO_2 is defined as the change from baseline (initiation of treatment for active subjects or completion of patient interface setup for control subjects) through 72 hours post-randomization, and over the first 7 days of life. Change in transcutaneous PCO_2 is defined as the change from baseline (initiation of treatment for active subjects or completion of patient interface setup for control subjects) through 72 hours post-randomization. Change in transcutaneous SpO_2 is defined as the change from baseline (initiation of treatment for active subjects or completion of patient interface setup for control subjects) through 72 hours post-randomization.

4.3 Missing Data

Missing values represent a potential source of bias in a clinical trial. Hence, every effort will be undertaken to fulfill all the requirements of the protocol concerning the collection and management of data; however, some missing data is inevitable. No imputation, including last observation carried forward, will be done for the any parameters; only available data will be considered.

4.4 Subgroup Analyses

Presentations by subgroup (sex, race, ethnic origin, country/region) or by gestational age strata will not be performed due to the small number of subjets enrolled.

5 TECHNICAL PERFORMANCE OF THE DEVICE

The technical performance of the device will be summarized for each active treatment. The incidence of the following will be summarized: total treatment duration, total amount dispensed, number of pauses, total time paused, ventilator/CPAP tubing detachments, aerosol tube detachments, aerosol tube condensate obstruction, proximal pressure port obstructions, (the number of the detachments that are intentional and uninterntional will also be recorded), study drug leakage (either liquid or aerosol) before the subject interface, occurrence of any alarm signals (before, during, and after dosing), automatic system shutdowns, , inability to maintain nCPAP (with a description), occurrence of any error codes, ADS temperature alerts (high or low). In addition, the weight and/or volume of liquid in all traps will be summarized as continuous variables. Statistical comparisons between active treatment groups are not planned.

Incomplete treatments with reasons and/or explanations will be listed.

6 SAFETY ANALYSES

6.1 Safety Population

The safety population is defined as all subjects who received any study medication, active or sham. Subjects will be included in the treatment group for the treatment actually received (if different than the group that they were randomized). The subjects enrolled open-label with active treatment (the first 2 subjects from each site) will be pooled with data from double-blind portion of the study. All safety assessments will be based on this population.

Safety analyses will be summarized by all subjects combined and by country or region.

6.2 Extent of Exposure

All subjects randomized to active treatment are to receive at least one dose of study medication. Subjects will receive two consecutive 50 minutes of aerosolized lucinactant in the first dose. The number of subjects who receive a repeat dose (50 minutes), the number of doses received, the amount of treatment received (based on time of treatment), and the number of subjects whose study treatment is terminated early will be summarized.

6.3 Adverse Events

All treatment-emergent AEs (TEAEs; AEs occurring at or after randomization) will be coded by preferred term and system organ class (SOC) from the Medical Dictionary for Regulatory

Activities (MedDRA), version 16.1 or above, and will be reviewed by the medical monitor or designee. All TEAEs will be summarized as categorical variables (frequency and percent) by treatment group unless otherwise indicated. TEAEs that are related to the device (ADEs) will be summarized with all AEs and separately. TEAEs will not be compared between treatment groups.

6.3.1 Peri-Dosing AEs

The incidence of peri-dosing events (ie, bradycardia, desaturation, gagging/regurgitation, apnea, and pallor) will be summarized.

In addition, the incidence of complications related to the placement of bi-nasal prongs (bleeding, apparent obstruction to the nares, occlusion of the prongs, nasal irritation, and other) will be summarized by treatment group.

6.3.2 AEs Related to Surfactant Administration (AEs of Special Interest)

Individual air leaks (eg, pneumothorax, pulmonary interstitial emphysema, pneumo-mediastinum, pneumopericardium, and subcutaneous emphysema) will be identified by medical review of all AEs and summarized by treatment group.

Occurrences of apnea, bradycardia, and desaturation after the peri-dosing period will be summarized by treatment group.

6.3.3 Other TEAEs

TEAEs, other than those listed above, will be summarized by treatment group by the MedDRA preferred term and SOC for all TEAEs, regardless of relationship to study drug, and for TEAEs at least remotely related. If a TEAE occurs multiple times for the same subject within the same term or body system, only the most severe occurrence for that term or body system will be counted.

In addition, all TEAEs will be summarized by severity (mild, moderate, severe), relationship to the study drug (unrelated, unlikely related, possibly related, related), whether or not the TEAE was device related, and, if sufficient number of subjects warrant, by gender, race, and ethnic origin.

6.3.4 Serious Adverse Events

All SAEs, including multiple occurrences, will also be listed, to include severity, relationship to the study drug, gender, race, and ethnic origin.

6.3.5 Unexpected Adverse Device Effects

Unexpected adverse device effects (UADEs) will be listed and summarized by treatment group using frequency counts and percentages. If the same UADE occurs multiple times for the same subject, the most severe occurrence will be counted.

6.3.6 Deaths

All-cause mortality and deaths due to RDS during the study will be summarized by treatment group using frequency counts and percentages. Deaths by subject will also be listed and will include primary cause, date and time of death, gender, race, and ethnic origin.

6.4 Clinical Assessments of Safety

6.4.1 Vital Signs

Vital signs, including body temperature, respiration rate, and heart rate, will be summarized at all pre-specified time points. Clinically significant vital signs will also be recorded as AEs.

6.4.2 Physical Examination

For each body system evaluated at screening and at the final physical examination, frequency counts and percentages of normal and abnormal results will be summarized by treatment group. In addition, a shift table to describe the changes in normal/abnormal results between screening and the final visit will be presented. Any new abnormal physical examination findings must be documented as AEs.

6.4.3 Respiratory Support and Supplemental Oxygen

Pressure support, including respiratory rate, CPAP, and FiO_2 (as appropriate) at all time points will be summarized as continuous variables. For subjects receiving mechanical ventilation (MV) through Day 7, the mode, mean airway pressure (MAP), respiratory rate, and FiO_2 will be summarized. For subjects receiving supplemental oxygen through Day 7, the mode and the FiO_2 will be summarized. All MV and supplemental oxygen data, including other settings (eg, tidal volume, PIP, PEEP, flow rate, mode of delivery) will be listed by subject.

The number of subjects requiring respiratory support in the delivery room, including sustained inflation, will be summarized using frequency and percent.

6.5 Long-Term Follow-Up

No longer applicable.

7 INTERIM ANALYSES AND DATA MONITORING

7.1 Data Monitoring Committee

The purpose of the DMC is to evaluate the degree of risk involved in study subject participation within each treatment group and to determine if study continuation in accordance with the current protocol holds the potential to institute any undue harm, or threat to the safety and welfare of study subjects. The DMC will consist of 3 to 5 experts in the field of RDS; at least 2 of the experts must be neonatologists. During the conduct of the study, safety summaries were provided to the DMC chairperson. No safety concerns were identified.

Since the study terminated before the scheduled meeting of the DMC, no further action from the DMC is required.

7.2 Interim Analyses/DMC Meetings

During the primary phase (screening to 36 weeks PMA), the chair of the DMC will receive regular reports on SAEs and AEs of interest. There was one planned meeting during study conduct; however, this was cancelled as the study was terminated early.

7.3 Data Monitoring

The data will be entered into a validated database. Members of Windtree's Data Management department are responsible for data processing, in accordance with procedural documentation. 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.

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.

8 STATISTICAL TECHNICAL ISSUES

8.1 Methods of Assigning Subjects to Treatment Groups

Subjects will be assigned to receive either 160 mg TPL/kg lucinactant for inhalation in conjunction with nCPAP or control (sham treatment). Preterm neonates who successfully meet all eligibility criteria will be randomly assigned within their applicable stratum (26 to 28 completed weeks PMA or 29 to 32 completed weeks PMA) to one of the 2 treatment groups in a 1:1 ratio. Subjects will be randomized/enrolled using centralized allocation electronically (eg, interactive response technology [IRT]), including the open-label subjects (the first 2 subjects at each site). Neonates from multiple births will be randomized independently. Randomization information will be provided to the study drug preparer (eg, pharmacist). The PI, study staff (eg, site coordinator) (as applicable), and attending physicians as appropriate will be masked to the treatment assignment, as described in the site's blinding/masking plan. Infants who are randomized and on study nCPAP but no longer meet qualification criteria before treatment will still receive the study treatment, unless it is unsafe to do so in the opinion of the investigator.

8.2 Blinding/Masking

In order to minimize bias in subject assessments, study treatment masking will be employed. Details on blinding can be found in the Blinding Plan for 03-CL-1702.

8.3 Details on Statistical Methods

Only summary statistics will be employed. No statistical testing will be done.

8.4 Multiplicity

Not applicable.

9 GENERAL ANALYSIS DEFINITIONS

All summaries and statistical analyses will be generated using SAS® System for Windows™, version 9.1 or higher.

9.1 Baseline Definition

Baseline is defined as the measurement at the start of study drug administration for subjects randomized to the active group, and time of patient interface change for subjects randomized to the control group (both recorded as "initiation of study treatment" on several forms).

9.2 Windows for Visits

Accurate clock times will be recorded for each timed event in military time (24-hour clock). Day 1 is the day on which randomization occurs; Day 2 begins at midnight following randomization; Day 3 is the 2nd day following randomization; Day 28 will be the 27th day after the day of randomization.

All assessments at pre-specified time points are to be conducted within the windows specified in the protocol. The windows for the the 6-month and 12-month visits will be ±2 weeks (not specified in protocol). Summary tables will use the pre-specified time points, not the actual times, to summarize the data.

9.3 Site Pooling Methods

Pooled centers will not be used.

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11 LIST OF SUMMARY TABLES, LISTINGS, AND FIGURES

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