2. SYNOPSIS

Name of Sponsor/Company:	**Name of Finished Product:**	**Name of Active Ingredients:**
Windtree Therapeutics, Inc. (formerly Discovery Laboratories, Inc.) 2600 Kelly Road Suite 100 Warrington, PA 18976, USA	AEROSURF™ (lucinactant for inhalation) Lucinactant 30 mg TPL/ml (reconstituted)	Dipalmitoylphosphatidylcholine (DPPC), palmitoyloleoyl-phosphatidylglycerol sodium salt (POPG, Na), palmitic acid (PA), and sinapultide (KL_4-peptide)

Title of Study:

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

Investigators and Study Centers:

A total of 22 investigators from the United States (US), Canada, Chile and Poland received institutional review board (IRB), research ethics board (REB), or ethics committee (EC), and sponsor approval for participation in this study; subjects were enrolled at 15 study centers. The names of the investigators, addresses of the study centers, and copies of the investigators' curricula vitae are provided in Appendix 16.1.4.

Publication (reference):

None

Study Period:	**Phase of Development:**
15 January 2016 – 08 July 2017 The study was terminated early on 08 July 2017	2a

Objectives:

The primary objective of this study was to evaluate the safety and tolerability of lucinactant for inhalation, administered as an aerosol in 4 escalating doses to a preterm, neonatal population 26 to 28 completed weeks post-menstrual age (PMA) receiving nasal continuous positive airway pressure (nCPAP) for respiratory distress syndrome (RDS) compared with neonates receiving nCPAP alone. Safety and tolerability were evaluated using the same measures and assessments that were used in Study 03-CL-1201, in which lucinactant for inhalation was shown to be generally safe and well-tolerated in neonates 29 to 34 completed weeks PMA.

Methodology:

This multicenter, randomized, controlled, open-label, dose-escalation study, was conducted to evaluate the safety and tolerability of lucinactant for inhalation in conjunction with nCPAP in comparison with nCPAP alone in preterm neonates 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 prototype investigational delivery device, AEROSURF™ Delivery System (ADS). Reconstituted lyophilized lucinactant was aerosolized by the investigational device, ADS (using the capillary aerosol generator [CAG]), and introduced into the nCPAP circuit. Those randomized to the control arm continued to receive nCPAP alone. Dose assignments were unblinded, as the primary objective of this study was safety and tolerability. Preliminary efficacy endpoints were assessed as an exploratory objective.

Preterm neonates between 26 and 28 completed weeks PMA who were within the first 20 hours after birth and who had successful implementation of controlled nCPAP within 90 minutes of birth were considered to be potential subjects. Before study enrollment, legal guardians were provided a written informed consent form (ICF) for each potential

Name of Sponsor/Company:	**Name of Finished Product:**	**Name of Active Ingredients:**
Windtree Therapeutics, Inc. (formerly Discovery Laboratories, Inc.) 2600 Kelly Road Suite 100 Warrington, PA 18976, USA	AEROSURF™ (lucinactant for inhalation) Lucinactant 30 mg TPL/ml (reconstituted)	Dipalmitoylphosphatidylcholine (DPPC), palmitoyloleoyl-phosphatidylglycerol sodium salt (POPG, Na), palmitic acid (PA), and sinapultide (KL_4-peptide)

subject. Qualification for study enrollment was established after confirmation that the subject had met all of the inclusion criteria and none of the exclusion criteria. The clinical criteria for enrollment could have been met prior to informed consent being obtained; however, no study-specific procedures that were not part of the usual standard care of the subject at the institution were performed until informed consent was provided by a legally authorized representative of the subject. Inclusion criteria to be met within the first 20 hours after birth included a required nCPAP of 5 to 6 cm H_2O and a fraction of inspired oxygen (FiO_2) within a range of 0.25 to 0.50 for at least 30 minutes to maintain oxygen saturation as determined by pulse oximetry (SpO_2) of 88% to 95%.

As soon as study eligibility was confirmed and the informed consent was signed, subjects were randomized in a 1:1 ratio to either an active arm, to receive lucinactant for inhalation (1 of 4 intended dose groups enrolled sequentially) in conjunction with nCPAP, or a control arm, who received nCPAP alone. Doses of lucinactant for inhalation in each respective dosing group (Dosing Groups I through IV) were planned to be 50, 75, 100, or 150 mg total phospholipids (TPL)/kg administered over 30, 45, 60, or 90 minutes, respectively, and were administered within 2 hours of randomization. The study was terminated for administrative reasons (including resource limitations and the intent to study the 26-28 GA weeks PMA patients in an amendment to Study 03-CL-1202). Subjects were eligible to receive a repeat dose between 2 and 24 hours after the initial dose if subjects met repeat dosing criteria. The dose varied by the volume of the nominal dose of reconstituted lucinactant (30 mg TPL/ml) aerosolized and introduced into the nCPAP circuit, given over a predetermined time for each dose.

After completion of enrollment of Dosing Group I and all subjects completed Study Day 7, a safety assessment (study-related adverse events [AEs], including adverse device effects [ADEs], serious adverse events [SAEs], and additional safety endpoints) was performed by an independent safety review committee (SRC). Following completion of enrollment within the dosing group, the lucinactant for inhalation dose was escalated for Dosing Group II (75 mg TPL/kg) and dosing Group III (100 mg TPL/kg). Subjects were followed through 36 weeks PMA, neonatal intensive care unit (NICU) discharge, hospital transfer, or death, whichever came first. The final study visit occurred at 36 weeks PMA or at time of discharge/transfer for all subjects.

All enrolled subjects received 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. Neonates in the NICU are continuously monitored using advanced and sophisticated monitoring equipment, and there is ready and immediate access to equipment, medications, and skilled personnel that may be needed to address emergent developments. Interventions such as endotracheal intubation, mechanical ventilation, and surfactant administration were readily available to all study subjects if clinically indicated in accordance with the high level standard of care customary in the NICU.

Number of Subjects (estimated and actual):

Number estimated: Approximately 64
Number enrolled/treated: 48/48
Number completing study: 48
Number discontinued: 0
Number discontinued due to adverse event (AE): 0

Name of Sponsor/Company:	**Name of Finished Product:**	**Name of Active Ingredients:**
Windtree Therapeutics, Inc. (formerly Discovery Laboratories, Inc.) 2600 Kelly Road Suite 100 Warrington, PA 18976, USA	AEROSURF™ (lucinactant for inhalation) Lucinactant 30 mg TPL/ml (reconstituted)	Dipalmitoylphosphatidylcholine (DPPC), palmitoyloleoyl-phosphatidylglycerol sodium salt (POPG, Na), palmitic acid (PA), and sinapultide (KL_4-peptide)

Diagnosis and Main Criteria for Entry:

The study population consisted of preterm neonates from 26 to 28 completed weeks PMA with RDS. Subjects who met all of the following entry criteria were eligible for the study:

1. Signed ICF from legally authorized representative;
2. Gestational age 26 to 28 completed weeks (28 weeks, 6 days) 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, required an nCPAP of 5 to 6 cm H_2O and a FiO_2 of 0.25 to 0.50 that was clinically indicated for at least 30 minutes to maintain SpO_2 of 88% to 95%. Transient (<10 minutes) FiO_2 excursions below 0.25 or above 0.50 did not reset the 30 minute requirement.

Test Product, Dose and Mode of Administration, and Batch Numbers:

Reconstituted lyophilized lucinactant (30mg TPL/ml) was aerosolized by the prototype ADS (using CAG technology), and introduced into the nCPAP circuit. Those randomized to the control arm continued to receive nCPAP alone. The exposure time was based on the nominal dose. The nominal dose is the amount of lucinactant aerosolized by the ADS. 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 is the amount of the emitted dose that is likely to be inhaled, is estimated by product of the aerosol concentration, the minute ventilation of the neonate, and the administration time of the aerosol.

Subjects randomized to the active study arm received aerosolized reconstituted lucinactant, in conjunction with nCPAP, within 2 hours of randomization through the ADS at 1 of 4 planned doses (50, 75, 100, or 150 mg TPL/kg) administered over 30, 45, 60, or 90 minutes, respectively, as shown below.

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 was allowed if repeat dosing criteria were 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 was allowed if repeat dosing criteria were 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 was allowed if repeat dosing criteria were 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 was allowed if repeat dosing criteria were met. Control Arm (n = 8): Continuous nCPAP

Name of Sponsor/Company:	**Name of Finished Product:**	**Name of Active Ingredients:**
Windtree Therapeutics, Inc. (formerly Discovery Laboratories, Inc.) 2600 Kelly Road Suite 100 Warrington, PA 18976, USA	AEROSURF™ (lucinactant for inhalation) Lucinactant 30 mg TPL/ml (reconstituted)	Dipalmitoylphosphatidylcholine (DPPC), palmitoyloleoyl-phosphatidylglycerol sodium salt (POPG, Na), palmitic acid (PA), and sinapultide (KL_4-peptide)

The study was terminated prior to subject enrollment for Dosing Group IV by the sponsor for administrative reasons (including resource limitations and the intent to study the 26-28 GA weeks PMA patients in an amendment to Study 03-CL-1202).

The lot/batch numbers of lyophilized lucinactant for each dose (50, 75, and 100 mg TPL/kg) were as follows:

All dosing groups included lots G15001 and G15003.

Study Duration:

First enrollment to last enrollment: 15 January 2016 to 14 May 2017. The planned duration of the study was from randomization through 36 weeks PMA, death, transfer, or discharge, whichever came first. The last subject's last visit was on 08 July 2017.

Reference Therapy, Dose and Mode of Administration, and Batch Numbers:

Subjects randomized to the control arms in all Dosing Groups received nCPAP alone. A total of 8 subjects were planned in each control arm of Dosing Groups I through IV; however, no subjects were enrolled in Dosing Group IV as the study was terminated by the sponsor for administrative reasons (including resource limitations and the intent to study the 26-28 GA weeks patients in an amendment to Study 03-CL-1202). Batch numbers are not applicable.

Criteria for Evaluation:

Efficacy (Exploratory):

Exploratory efficacy endpoints included the incidence of BPD, rate of survival without BPD at 36 weeks PMA, worsening of respiratory status (categorized as early if occurring ≤72 hours after birth or late if occurring >72 hours and ≤7 days after birth), and technical performance of the ADS (characterized indirectly through the subject's response to treatment and solicited feedback from the principal investigators [PIs] and relevant site-based study staff), physiological parameters (eg, FiO_2, PCO_2).

Results for subjects without treatment interruptions and time to and incidence of intubation are described.

Safety:

The primary endpoints of this study were derived from the safety evaluations reported from the time of randomization until 36 weeks PMA, death, transfer, or discharge, whichever came first. Safety endpoints included the following: survival (date of time of death, if applicable); AEs (including nasal excoriations by examination, evidence of lung air leak [eg, pneumothorax and pneumomediastinum], peri-dosing events [eg, bradycardia, desaturation, gagging/regurgitation, apnea, and pallor], and complications related to the placement of bi-nasal prongs); signs consistent with worsening respiratory status; concomitant medications; use of respiratory support and supplemental oxygen; complications of prematurity (eg, intraventricular hemorrhage [IVH], periventricular leukomalacia [PVL], pulmonary hemorrhage, necrotizing enterocolitis [NEC], patent ductus arteriosus [PDA],

Name of Sponsor/Company:	**Name of Finished Product:**	**Name of Active Ingredients:**
Windtree Therapeutics, Inc. (formerly Discovery Laboratories, Inc.) 2600 Kelly Road Suite 100 Warrington, PA 18976, USA	AEROSURF™ (lucinactant for inhalation) Lucinactant 30 mg TPL/ml (reconstituted)	Dipalmitoylphosphatidylcholine (DPPC), palmitoyloleoyl-phosphatidylglycerol sodium salt (POPG, Na), palmitic acid (PA), and sinapultide (KL_4-peptide)

sepsis, retinopathy of prematurity [ROP], and bronchopulmonary dysplasia [BPD]); physical examinations; tolerability of lucinactant for inhalation; incidence leading to withdrawal from study; arterial carbon dioxide (PCO_2) values, serum electrolyte measurements, body weight, vital signs, gastric liquid volume, defecation, SpO_2, and chest radiography.

Statistical Methods:

The statistical analyses of both the primary and secondary safety and tolerability objectives were based on all randomized preterm neonates in the study. In addition, data from all evaluable preterm neonates were analyzed for efficacy signals as an exploratory endpoint.

All safety endpoint data captured from randomization to completion of Study Day 7 for active subjects, and all available safety endpoint data for nCPAP only subjects, were evaluated by the SRC. As this is an open-label study with no hypothesis testing, no adjustments for p-values were required or employed for the interim analysis.

In addition, time to and incidence of intubation was added as an exploratory efficacy endpoint, and an analysis of subjects without treatment interruptions was added due to the unforeseen frequency of interruptions.

Results:

A total of 402 subjects 26-28 weeks GA were screened and 48 subjects (24 in the active groups and 24 in the nCPAP only group) were randomized into the study from 15 sites in 4 countries (US, Canada, Chile, and Poland). Subjects were typically white (32 [67%]) and not Hispanic (35 [73%]), with a mean gestational age of 27.3 and 27.5 weeks for active and nCPAP only groups, respectively. Approximately half of the subjects were male in the active group (11 [46%]); more than half were male in the nCPAP only group (16 [67%]).

All 48 randomized subjects received treatment. Most subjects in the 50 and 100 mg TPL/kg received their full doses (7 [88%] and 6 [75%], respectively). Only 3 subjects in the 75 mg TPL/kg group received their full initial or repeat dose. In almost all cases, receiving less than a full dose was as a result of treatment interruptions. Interruptions primarily occurred due to surfactant clogged filters in the disposable components of the prototype ADS, and were more likely to occur in the 45 minute (ie, longer) treatments. No treatment interruptions resulted in loss of inspiratory flow or inability to maintain nCPAP.

Efficacy:

For this study, efficacy was considered an exploratory analysis. The primary purpose of the efficacy analysis was to determine the feasibility of certain efficacy measurements and to determine if there was any physiological evidence of aerosol delivery to the lungs; no statistical calculations or comparisons were planned.

A total of 6 subjects (25%) in the nCPAP only group and no subjects in the active group developed BPD during the study. A post hoc statistical comparison was conducted using Chi-square which resulted in a p-value of 0.022.

Overall, worsening of respiratory status occurred at comparable rates in active subjects (79%) vs. nCPAP only subjects (75%), and the individual criteria defining this endpoint occurred at a similar rate between the active groups and the nCPAP only group, with the exception of need for additional surfactant therapy and worsening respiratory

Name of Sponsor/Company:	Name of Finished Product:	Name of Active Ingredients:
Windtree Therapeutics, Inc. (formerly Discovery Laboratories, Inc.) 2600 Kelly Road Suite 100 Warrington, PA 18976, USA	AEROSURF™ (lucinactant for inhalation) Lucinactant 30 mg TPL/ml (reconstituted)	Dipalmitoylphosphatidylcholine (DPPC), palmitoyloleoyl-phosphatidylglycerol sodium salt (POPG, Na), palmitic acid (PA), and sinapultide (KL_4-peptide)

status. By definition, need for additional surfactant therapy was reported only for subjects in the active treatments; this question was not applicable for subjects in the nCPAP only group. Worsening respiratory status was determined by the PI for 6 (25%) of the nCPAP only subjects and for 1 (4%) of the active subjects. Intubation was generally similar between the treatments (17 [71%] vs. 16 [67%] for active and control, respectively). If only subjects without treatment interruptions are considered, the rate of intubation for active subjects drops to 63% (4/7 [57%], 3/3 [100%], and 3/6 [50%] for 50, 75, and 100 mg TPL/kg, respectively). The median time until intubation due to nCPAP failure was slightly higher in the active groups (median of 8.9 hours) compared to the nCPAP only group (median of 5.8 hours).

Baseline values for physiological measurements were similar in active subjects (mean FiO_2 of 0.34 and PCO_2 of 48.9 mmHg) and nCPAP only subjects (mean FiO_2 of 0.32 and PCO_2 of 50.5 mmHg).

Over the 72-hour measurement period, there appears to be a dose-response for subjects in the 75 and 100 mg TPL/kg groups in decreases from baseline in FiO_2 values (approximately 10% decrease), whereas subjects in the nCPAP only group did not show a similar decrease (less than 5% decrease). No trends or consistent changes were noted for PCO_2 for any active treatment or control groups.

Technical performance of the ADS was considered adequate. One detachment (noted before aerosol delivery began), and 1 incident of leakage was noted. No incidents of airway tubing obstructions, loss of inspiratory flow, or inability to maintain nCPAP were reported. There were 8 subjects with reports of automatic system shutdowns in the initial dose (1 for 50 mg TPL/kg, 4 for 75 mg TPL/kg and 3 for 100 mg TPL/kg) and 5 subjects with reports in the repeat dose (all for the 75 mg TPL/kg group). Automatic system shutdowns were predominantly due to an in-line filter clogging and the system responded appropriately in these cases.

Safety:

Lucinactant for inhalation was generally well-tolerated.

All subjects experienced at least one AE. The most common TEAEs were neonatal apnea (17 [71%] and 19 [79%] subjects for active and nCPAP only groups, respectively), neonatal anemia (12 [50%] and 13 [54%]), desaturation (12 [50%] and 9 (38%), patent ductus arteriosus (10 [42%] and 10 [42%]), and neonatal jaundice (9 [38%] and 11 [46%]). Most TEAEs were consistent between active and nCPAP only, with no differences exceeding 4 subjects in either direction, with the exception of dermatitis diaper (7 [29%] for active vs. 1 [4%] for control), retinopathy of prematurity (4 [17%] for active vs. 9 [38%] for control), and bronchopulmonary dysplasia (0 for active vs. 7 [29%] for control). One case of BPD reported as an adverse event, in the nCPAP only group, was not included in the BPD analysis as this subject was not on supplemental oxygen at 36 weeks PMA. The number of subjects with air leaks, which were an AE of special interest, was similar between active (5 [21%]) and nCPAP only (4 [17%]). For the air leak of pneumothorax, there were 2 (8%) active subjects compared to 3 (13%) control subjects reported.

Peri-dosing AEs were experienced by 7 (29%) subjects, and related AEs were experienced by 9 (38%) subjects which, by definition, could only occur for subjects in the active group. No subjects reported complications related to the placement of bi-nasal prongs during the dosing period. There were two events reported as ADEs: one report of

Name of Sponsor/Company:	**Name of Finished Product:**	**Name of Active Ingredients:**
Windtree Therapeutics, Inc. (formerly Discovery Laboratories, Inc.) 2600 Kelly Road Suite 100 Warrington, PA 18976, USA	AEROSURF™ (lucinactant for inhalation) Lucinactant 30 mg TPL/ml (reconstituted)	Dipalmitoylphosphatidylcholine (DPPC), palmitoyloleoyl-phosphatidylglycerol sodium salt (POPG, Na), palmitic acid (PA), and sinapultide (KL_4-peptide)

nasal inflammation (50 mg TPL/kg) and one report of desaturation (100 mg TPL/kg). Both ADEs, which were not serious, were considered mild, with the nasal inflammation reported as unrelated and the desaturation reported as related.

There were SAEs experienced by 9 (38%) subjects in the active group and 6 (25%) in the nCPAP only group. One active subject (50 mg TPL/kg) had an SAE that was considered possibly related to study drug treatment. The other active subjects had SAEs that were considered unlikely related or not related to study drug treatment.

There were 2 deaths in this study: 1 in the 50 mg TPL/kg group and 1 in the 75 mg TPL/kg group. The 2 deaths were considered unlikely related or not related, respectively, to study drug treatment. One death was as a result of pneumoperitoneum (Subject 11011, 75 mg TPL/kg, day-of-life [DOL] 10) and the other due to NEC and bowel perforation (Subject 12014, 50 mg TPL/kg, DOL 38).

Overall, there were no treatment-related trends observed in physical examination findings or changes from baseline. In addition, there were no meaningful differences for temperature, respiratory rate, or heart rate at any of the selected time points.

Approximately half (46%) of subjects on either active treatment or control received brief (< 10 minutes) positive pressure ventilation in the delivery room (DR).

After dosing, there were no clinically significant differences between active and nCPAP only subjects for MV, supplemental O_2, CPAP settings, or complications of prematurity.

Name of Sponsor/Company:	**Name of Finished Product:**	**Name of Active Ingredients:**
Windtree Therapeutics, Inc. (formerly Discovery Laboratories, Inc.) 2600 Kelly Road Suite 100 Warrington, PA 18976, USA	AEROSURF™ (lucinactant for inhalation) Lucinactant 30 mg TPL/ml (reconstituted)	Dipalmitoylphosphatidylcholine (DPPC), palmitoyloleoyl-phosphatidylglycerol sodium salt (POPG, Na), palmitic acid (PA), and sinapultide (KL_4-peptide)

Discussion and Overall Conclusions:

15 January 2016 – 08 July 2017

From 15 January 2016 to 08 July 2017, 48 preterm neonates 26 to 28 weeks PMA participated in this study. Baseline demographic and clinical characteristics of each group were generally similar between treatment groups

Safety evaluations included assessment of AEs during dosing (peri-dosing events), AEs, ADEs, and SAEs that occurred throughout the duration of the study. No clinically relevant differences in AEs were noted for subjects in the active groups compared with subjects in the nCPAP only group. There were 2 deaths reported, considered by the PI to be unlikely related or not related to study drug treatment. Lucinactant for inhalation appeared to be well tolerated at all doses administered.

The prototype ADS functioned as intended; however, an unanticipated high number of treatment interruptions was noted, mostly due to clogging of an in-line filter. When clogging occurred, the device functioned as designed and ceased aerosol delivery. Nonetheless, the use of the ADS for the delivery of reconstituted lucinactant in the study population and setting did not reveal any safety concerns.

Exploratory efficacy assessment suggested that treatment with lucinactant for inhalation decreases the FiO_2 requirements, increases time to intubation, and decreases BPD in preterm neonates 26 to 28 weeks gestation PMA with RDS. When the dose is delivered as intended without treatment interruptions, CPAP failures and intubations may be reduced.

Results of this study support further development of lucinactant for inhalation.

Date of Report: 01 November 2017