2. SYNOPSIS

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

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

Investigators and Study Centers:

A total of 52 investigators from the United States (US), Canada, Poland, Netherlands, Ireland, Hungary, Chile, and Colombia received institutional review board (IRB), research ethics board (REB), ethics committee (EC), and sponsor approval for participation in this study. A total of 47 investigators enrolled subjects. 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:**
14 April 2016 – 06 August 2019	2b

Objectives:

The objectives of this study were to evaluate the safety and efficacy of lucinactant for inhalation in conjunction with nCPAP, in comparison to nCPAP alone, in preterm neonates with RDS, as assessed by the incidence of and time to respiratory failure and/or death due to RDS in the first 72 hours of life, the incidence of bronchopulmonary dysplasia (BPD) at 36 weeks PMA, and change in physiologic parameters (fraction of inspired oxygen [FiO_2] and partial pressure of carbon dioxide [PCO_2]) over the first 72 hours of life.

Methodology:

This study was a multinational, multicenter, masked, randomized, controlled study to evaluate the safety and efficacy of 2 different dosages of lucinactant for inhalation (40 mg TPL/kg and 80 mg TPL/kg) in conjunction with nCPAP compared with nCPAP alone, in preterm neonates 26 to 32 completed weeks PMA who were cared for in a neonatal intensive care unit (NICU) and who were within the first 20 hours after birth, who had successful implementation of non-invasive respiratory support or ventilation within 90 minutes of birth, and who were candidates for SRT. The preferred initial mode of support was study nCPAP; however, other modes of non-invasive ventilation were acceptable if the investigator felt it was safe to switch the subject to study nCPAP following consent and screening. There were 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 was to be analyzed and reported at the completion of each study phase.

Before study enrollment, legal guardians provided a signed written informed consent form (ICF) for each potential subject. Qualifications for study enrollment were established after confirmation that the subject had met all of the

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inclusion criteria and none of the exclusion criteria. The clinical criteria for enrollment may 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 to be performed until the informed consent had been provided by a legally authorized representative of the subject.

Inclusion criteria to be met within the first 20 hours after birth included respiratory insufficiency with a requirement for nCPAP of 5 to 7 cm H_2O with a $FiO_2 \geq 0.25$ (> 0.21 for neonates 26-28 weeks PMA) to 0.4 to maintain oxygen saturation measured by pulse oximetry (SpO_2) of 90% to 95% for at least 30 minutes. As soon as study qualification had been confirmed and the informed consent was signed, subjects were randomized to 1 of the 2 active treatment groups or to the control group (nCPAP only with simulated ["sham"] study drug treatment). Study treatment (lucinactant for inhalation or sham/control) must have been initiated as soon as possible after randomization.

Subjects were eligible to receive up to 2 repeat doses of the treatment to which they were originally assigned. Repeat doses were given as soon as 2 hours from completion of the previous dose up to 36 hours after completion of randomization if subjects met repeat dosing criteria (as described in the "Treatment Groups" section) unless it was unsafe to do so in the judgment of the investigator. Subjects randomized to the control group continued on nCPAP alone but received repeated sham treatments to maintain study masking.

All subjects in the active treatment groups received the same drug concentration of lucinactant for inhalation (30 mg TPL/mL) at the same rate of delivery (aerosol concentration of 4.2 mg TPL/L in aerosol carrier gas flow of 3 L/min). The dosages varied by the predetermined administration time for each dose (25 minutes for the 40 mg TPL/kg arm, 50 minutes for the 80 mg TPL/kg arm). Lucinactant for inhalation was delivered by the investigational ADS device in conjunction with a commercially available nCPAP generator and patient interface. Dose assignments were masked from the principal investigator (PI), clinical and study staff (eg, site coordinator, bedside nurse) (as applicable); sponsor (as applicable); and subject's parents/legal guardians.

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

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

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Number of Subjects (estimated and actual):

Number estimated: Approximately 240
Number enrolled/treated: 221/213
Number completing study: 221
Number discontinued: 0
Number discontinued due to adverse event (AE): 0

Diagnosis and Main Criteria for Entry:

The study population consisted of preterm neonates from 26 to 32 completed weeks PMA with RDS. Each subject must have met all of the following inclusion criteria to be enrolled in this study:

1. Signed ICF from legally authorized representative
2. 26 0/7 to 32 6/7 completed weeks' gestation PMA
3. Successful implementation of non-invasive support or ventilation 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 7 cm H_2O with an $FiO_2 \geq 0.25$ (>0.21 for neonates 26-28 weeks PMA) to 0.4 that is clinically indicated for at least 30 minutes to maintain SpO_2 of 90% to 95%. Transient (<10 minutes) FiO_2 excursions outside this range do not reset the 30-minute requirement.

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

Subjects randomized to the active treatment groups were administered an investigational drug-device combination product, lucinactant for inhalation, in conjunction with nCPAP. Reconstituted lyophilized lucinactant (reconstituted with sterile water for injection) was aerosolized by the investigational ADS device and introduced into the nCPAP circuit.

The theoretical inhaled dose (in mg TPL/kg) can be controlled based on the duration of exposure to the aerosol. This inhaled dose is a function of the concentration of lucinactant in the aerosol, the amount of aerosol inhaled by the subject (estimated by the subject's minute ventilation, assuming that all gas inhaled by the subject contains the same concentration of aerosol), and the duration of exposure to the aerosol. Because of losses that occur as the lucinactant aerosol travels from the ADS to the patient interface, approximately 35% of the reconstituted lucinactant aerosolized by the ADS was emitted and was available to be inhaled.

Repeat doses were given ≥2 hours from completion of the previous dose up to 36 hours after completion of randomization if subjects had a sustained (≥30 minutes) need for FiO_2 above the qualifying FiO_2 for study enrollment (≥ 0.25 for neonates 29-32 weeks PMA, > 0.21 for neonates 26-28 weeks PMA) to maintain SpO_2 of 90% to 95%, unless it was unsafe to do so in the judgment of the investigator. Masking procedures for the initial dose were followed for repeat doses.

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Planned Test Product Treatments

40 mg TPL/kg	40 mg TPL/kg administered over 25 minutes in conjunction with nCPAP (n=80) Up to 2 repeat doses of 40 mg TPL/kg administered over 25 minutes given if repeat dosing criteria met.
80 mg TPL/kg	80 mg TPL/kg administered over 50 minutes in conjunction with nCPAP (n=80) Up to 2 repeat doses of 80 mg TPL/kg administered over 50 minutes given if repeat dosing criteria met.

The lot/batch numbers used were as follows:

USA: G15001, G15006, G15004; Canada: G15004; Europe: G15003, 15006; Chile: G15004; Colombia: 15004, 16002.

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

Subjects in the nCPAP Only group received nCPAP alone. Batch numbers are not applicable.

Subjects randomized to the control (nCPAP only) group continued to receive nCPAP alone; in order to maintain masking, "sham" study drug treatment was used: the ADS will be brought to the bedside but was not used, and no active study drug was administered.

Repeat dosing were given ≥2 hours from completion of the previous dose up to 36 hours after completion of randomization, as was described for the active treatments. Masking procedures for nCPAP Only for the initial dose were followed for repeat doses.

Planned Control Treatment

nCPAP Only	Continuous nCPAP (n = 80) with sham drug treatment Up to 2 repeat sham treatments given if repeat dosing criteria met.

Study Duration:

First enrollment to last enrollment: 14 April 2016 – 28 May 2017. The planned duration of the primary phase study was from randomization through 36 weeks PMA, death, transfer, or discharge, whichever came first. The last subject's last visit for the primary phase was on 14 July 2017. The one-year follow-up phase was completed on 06 August 2019.

Criteria for Evaluation:

Efficacy:

The primary endpoint for this study was time to respiratory failure or death due to RDS within the first 72 hours of life. A subject was categorized as having respiratory failure due to RDS if either of the following occurred:

1. Intubation for MV and/or surfactant administration within 72 hours of life

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2. The subject met at least 1 of the following criteria, regardless of whether endotracheal intubation was performed:
   a. A sustained (≥ 60 minutes) need for FiO_2 > 0.45 to maintain an SpO_2 > 90% to 95%;
   b. A sustained (on ≥ 2 consecutive observations > 60 minutes apart) transcutaneous PCO_2 > 65 mm Hg;
   c. nCPAP > 8 cm H_2O.

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

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

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

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

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

Safety:

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

1. Survival (date and time of death, if applicable);
2. AEs, including adverse device effects (ADEs) and AEs of special interest including peri-dosing events, complications related to placement of bi-nasal prongs, and air leak;
3. Concomitant medications;
4. Use of respiratory support and supplemental O_2, including the following:
   a. Need for endotracheal intubation and MV;
   b. Mode of respiratory support (including supplemental oxygen) and important parameters for that mode;
5. Complications of prematurity;
6. Physical examinations;
7. Tolerability of lucinactant for inhalation;
8. Incidence of air leak;
9. Assessments of the following:
   a. Vital signs;
   b. O_2 saturation, as determined by pulse oximetry (SpO_2);

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c. Serum electrolyte measurements;
d. Defecation;
e. Chest radiography prior to intubation.

Statistical Methods:

The statistical analysis of both the primary and secondary objectives was based on all enrolled preterm neonates. For the efficacy analysis, populations of all randomized subjects who received any treatment (intent-to-treat [ITT]) and subjects with no major protocol deviations (per-protocol) were evaluated, based upon the treatment group to which they were randomized. For the safety analysis, all subjects randomized to the control group or who received any lucinactant for inhalation (including partial doses) were evaluated, based upon the treatment they actually received. All analyses were performed for all subjects combined and by gestational age strata.

The treatment difference (delta) between active and control treatments was 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.

The data monitoring committee (DMC) conducted 2 preplanned interim analyses: 1) after approximately 25% of subjects had been enrolled and 2) after 66% of subjects had been enrolled. No safety concerns were identified during either review and the DMC determined to continue the study as planned.

Results:

A total of 221 subjects were enrolled into the study. Of these, 8 subjects did not receive study treatment (primarily due to being intubated between randomization and treatment). A total of 213 subjects 28 to 32 weeks PMA received study treatment and constitute both the modified Intent-to-Treat (primary efficacy population) and Safety populations. Baseline demographic and clinical characteristics of each group were generally similar between treatment groups.

Efficacy:

The endpoint of respiratory failure through 72 hours did not show any evidence of improvement for lucinactant for inhalation for both the primary population (modified intent-to-treat [mITT]) and the intent-to-treat population. The per-protocol population showed some evidence of improvement, with the incidence rate of 38% in the 80 mg TPL/kg group compared to an incidence rate of 44% in the nCPAP only group. Treatment interruptions, primarily due to filter clogging, may be partly responsible for why the expected efficacy response was attenuated. Specifically, when subjects were treated as intended, a 27% relative reduction in respiratory failure was evidenced (44% for CPAP alone vs. 32% for 80 mg TPL/kg) in the mITT population.

Additionally, there were indications of effect in time to respiratory failure, in the physiological measurements of FiO_2 and S/F ratio, and in incidence of BPD. While statistical significance was not achieved in these measurements, the fact

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that results consistently show numerical improvements for the 80 mg TPL/kg treatment group is some evidence of efficacy.

In this study, 28 subjects in the 80 mg TPL/kg group and 6 subjects in the 40 mg TPL/kg group experienced treatment interruptions that impacted study drug delivery, primarily due to a condition identified as "syringe pressure out of range." Syringe pressure out of range interruptions were unanticipated and have been extensively assessed. Thus, future iterations of the device will mitigate this condition, although other types of interruptions (eg, manual stoppage) will likely continue in the future. When lucinactant for inhalation is given as intended without treatment interruption, nCPAP failure and intubations appear to have been reduced in the 80 mg TPL/kg group compared to the nCPAP only group (14/44 [32%] for 80 mg TPL/kg and 31/71 [44%] for nCPAP only).

In summary, efficacy measurements did not meet the primary endpoint, but did provide some evidence of efficacy, especially if treatment interruptions are taken into account. Efficacy assessments suggested that treatment with lucinactant for inhalation may reduce intubation for mechanical ventilation and/or surfactant administration, decrease FiO_2, increase time to intubation, and decrease the incidence or severity of BPD in preterm neonates 28 to 32 weeks PMA with RDS.

Safety:

Lucinactant for inhalation was generally well tolerated. There were 3 deaths in this study, 1 in the 80 mg TPL/kg group and 2 in the nCPAP only group, neither of which was related to study drug treatment.

The vast majority of subjects experienced at least one AE. The incidence of TEAEs for the active groups compared with the nCPAP only group was generally similar, with the exception of a higher number of peri-dosing events, in particular desaturation, in the active groups and a higher number of sepsis in the nCPAP only group. Peri-dosing AEs were transient and generally mild. Complications of prematurity, including air leak, occurred at comparable rates between active and nCPAP only subjects, but was numerically higher in the nCPAP only group.

The ADS functioned as intended; however, a higher than expected number of treatment interruptions occurred due to clogging filters; this was especially prevalent in the 80 mg TPL/kg group, given the length of the treatment, where 28/72 subjects had at least 1 treatment that was prematurely interrupted by the device.

For different respiratory support modes, both non-invasive support and mechanical ventilation demonstrated that the time on those modes was less for active treatments than for nCPAP only. For time on supplemental oxygen (O_2 delivery without support), values were generally less for active treatment, although the median values for 80 mg TPL/kg and nCPAP only were similar.

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Long-Term Follow Up:

The long-term follow-up phase was completed on 06 August 2019. A total of 155 subjects completed the 12 months assessments. The assessment of any abnormality through 12 months were similar across the treatment groups, as was the case for body weight, length, and head circumference. The abbreviated neurological exam was similar for abnormalities, although the number of subjects with motor reflex or gross motor delay was slightly higher in the 80 mg TPL/kg and nCPAP only groups.

At the 6-month assessment, the number and percent of subjects that: experienced AEs (per protocol, specific AE information was not collected), used steroids/bronchodilators, were hospitalized, and/or that experienced a respiratory illness were similar between treatment groups. The assessment of subjects' overall health was also similar between groups, as was median time on nCPAP, supplemental oxygen, and MV. Similarly, at the 12-month assessment, there were few differences across treatment groups for the number and percent of subjects that experienced AEs, used steroids/bronchodilators, were hospitalized, and/or that experienced a respiratory illness. However, slightly more nCPAP only subjects experienced AEs, used steroids/bronchodilators, and experienced a respiratory illness compared to the 80 mg TPL/kg subjects. The assessment of subjects' overall health was similar between groups, and there were too few subjects receiving nCPAP, supplemental oxygen, and MV to compare between groups.

An assessment of any hospitalization from 36 weeks PMA through 12 months noted 25/58 (43%), 18/66 (27%), and 22/61 (36%) subjects in the 40 mg TPL/kg, 80 mg TPL/kg, and nCPAP only. The relative difference between subjects in the 80 mg TPL/kg and nCPAP only groups was a reduction of 24.4% in hospitalizations for the subjects in the 80 mg TPL/kg group. For subjects dosed as intended, the number of subjects in the 80 mg TPL/kg group is reduced to 9/40 (22.5%; relative reduction of 37.6%). 7

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Discussion and Overall Conclusions:

From 14 April 2016 to 14 July 2017, 221 preterm neonates 28 to 32 completed weeks PMA participated in this study. A total of 213 subjects received study treatment and constitute both the modified Intent-to-Treat (primary efficacy population) and Safety populations. Baseline demographic and clinical characteristics of each group were generally similar between treatment groups.

The endpoint of respiratory failure through 72 hours did not show any evidence of improvement for lucinactant for inhalation for both the primary population (modified intent-to-treat [mITT]) and the intent-to-treat population. The per-protocol population showed some evidence of improvement, with the incidence rate of 38% in the 80 mg TPL/kg group compared to an incidence rate of 44% in the nCPAP only group. It is believed that treatment interruptions, primarily due to filter clogging, are partly responsible for why the expected efficacy response was attenuated. In this study, 28 subjects in the 80 mg TPL/kg group and 6 subjects in the 40 mg TPL/kg group experienced treatment interruptions that impacted study drug delivery, primarily due to a condition identified as "syringe pressure out of range." Syringe pressure out of range interruptions were unanticipated and have been extensively assessed. When lucinactant for inhalation is given as intended (when subjects with treatment interruptions are removed from the mITT population), a 27% relative reduction in respiratory failure was evidenced (44% vs. 32%).

Efficacy assessments suggested that treatment with lucinactant for inhalation may reduce intubation for mechanical ventilation and/or surfactant administration, decrease FiO_2, increase time to intubation, and decrease the incidence of BPD in preterm neonates 28 to 32 weeks PMA with RDS.

There were 3 deaths in this study, 1 in the 80 mg TPL/kg group and 2 in the nCPAP only group, none of which were related to study drug treatment. The vast majority of subjects experienced at least one AE. The incidence of TEAEs for the active groups compared with the nCPAP only group was generally similar, with the exception of a higher number of events of desaturation in the active groups and a higher number of sepsis in the nCPAP only group. Peri-dosing AEs were transient and generally mild. Complications of prematurity, including air leak, occurred at comparable rates between active and nCPAP only subjects, but was numerically higher in the nCPAP only group.

In summary, efficacy measurements did not meet the primary endpoint, but did provide some evidence of efficacy, if treatment interruptions are taken into account, and in other efficacy parameters. For safety, lucinactant for inhalation was generally well-tolerated, and no specific safety concerns were noted. Results of this study indicate that further development of lucinactant for inhalation is warranted.

Date of Report: 11 June 2020