WINDTREE THERAPEUTICS, INC.

Statistical Analysis Plan

A Multicenter, Single-Treatment Study to Assess the Safety and Tolerability of Lyophilized Lucinactant in Adults with COVID-19 Associated Acute Lung Injury

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A Multicenter, Single-Treatment Study to Assess the Safety and Tolerability of Lyophilized Lucinactant in Adults with COVID-19 Associated Acute Lung Injury

Statistical Analysis Plan

Author/Project Biostatistician

Amy Lyu
Project Biostatistician

Date

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

Phillip D. Simmons
Executive Director, Biostatistics and Data Management

Date

Carlos Guardia, MD
Senior Medical Director

Date

EXECUTIVE SUMMARY

The primary objective of this study is to evaluate the safety and feasibility of lucinactant SRT in treating COVID-19, as assessed by OI at 12 hours post dosing and other physiological and outcome measurements through 24 hours or through Day 30. The secondary efficacy objective is to assess other measures of efficacy to ensure consistency of results across multiple endpoints.

This is a multicenter, single-treatment, safety pilot study. Subjects will consist of adults 18-75 (inclusive) with COVID-19 associated acute lung injury who are being cared for in a critical care environment. Up to 20 enrolled subjects will be administered an investigational drug product, lyophilized lucinactant. Reconstituted lyophilized lucinactant (reconstituted with sterile water for injection) will be delivered as a liquid into the trachea in quarter doses. Patients will be given injection of Lyophilized lucinactant 160 ml (~80 mg TPL/kg lean body weight of 30 mg/ml suspension), up to 3 repeat study treatments of the same dose volume may be given if criteria are met.

The DMC, made up of at least 3 experts in the field of infectious diseases, will 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.

During the treatment and post-dosing phases, the chair of the DMC will receive regular reports on SAEs and DMC members will be periodically updated on the program and trial status. An ad hoc meeting of the DMC will occur if the chair deems it necessary to address safety in the study. The DMC may recommend that study enrollment be suspended if safety concerns are identified or suspected.

Repeat study treatments of the same dose volume are allowed if patients meet the criteria. Up to 3 retreatment doses are allowed no sooner than 6 hours apart (from completion of previous dose). Subjects are eligible for retreatments if they remain on MV, there is no evidence of pneumothorax, the P/F ratio is under 300 (or S/F ratio is under 315, if no arterial line is present), and there are no safety concerns that would prevent retreatment (in the opinion of the investigator). Retreatments are given at the discretion of the investigator.

Study Duration:

For the treatment period (Day 1, from randomization to 24 hours after), post-treatment period (Days 2 to Day 5), and final period (Day 6 to Day 30), subjects will be followed for safety and

efficacy evaluations until the subject is 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 as the (lyophilized) lucinactant (n = 20). A final visit will occur at Day 30 or at the time of discharge or transfer (whichever occurs first) for all subjects. A subject is considered to have completed the study if he or she has completed all phases of the study, including the last scheduled procedure at Day 30.

Subject participation will be from enrollment to 30 days after enrollment, unless they have an ongoing SAE (to be followed for an additional 30 days). Subjects will be followed up to Day 30 at which time the subjects overall health will be assessed, a physical examination will be performed.

The end of the study is defined as completion of the last visit or procedure for the last subject in the trial (last subject/last visit). Overall, study enrollment will be completed in approximately 3 to 4 months, with the last subject last visit approximately 4-5 months from the time the first subject enrolled.

Endpoints:

The primary endpoints are safety and tolerability of reconstituted lyophilized lucinactant given as a bolus to patients with COVID-19 and change from baseline in OI at 12 hours post initiation of dosing. OI is defined as $P_{aw} \times FiO_2 \times 100/PaO_2$.

Secondary efficacy endpoints of the study includes:

- Change from baseline through 24 hours post dosing initiation:
  - FiO_2;
  - PaO_2;
  - SpO_2;
  - OI;
  - $PaCO_2$;
  - $ETCO_2$;
  - P/F and or S/F ratios, defined as PaO_2 or SpO_2 divided by FiO_2;
  - Plateau pressure and peak inspiratory pressure (PIP) measured on the ventilator;
  - Ventilation Index (VI). VI is defined as $[RR \times (PIP - PEEP) \times PaCO_2]/1000$;
  - Lung compliance;
  - Pressure-volume loops if ventilator technology permits.
- Through 30 days:
  - Daily lung compliance (static) on ventilator;

- Ventilator free days;
- Days in the intensive care unit (ICU);
- Days in the hospital;
- Incidence of all-cause mortality;
- Organ failure free days.

Safety Endpoints in the study are:

1. All-cause mortality;
2. Peri-dosing events (desaturation, bradycardia, ET reflux, hypotension)
3. AEs and serious AEs (SAEs). SAEs that are ongoing at Day 30 will be followed for an additional 30 days;
4. Air leaks as AEs of special interest;
5. Assessments of vital signs.

Analysis Populations:

The study population will be comprised of adults 18-75 (inclusive) who are positive for SARS-CoV-2, are exhibiting symptoms of severe COVID-19 infection, who are intubated and are receiving mechanical ventilation in a critical care environment

The objective of the pilot safety study is to evaluate the safety and feasibility of lucinactant administration in COVID-19 patients. A small number of patients should be sufficient to provide evidence that liquid lucinactant can be safely delivered as an intratracheal bolus. A total of up to 20 study subjects will be enrolled.

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ABBREVIATIONS

Abbreviation	Description
β-hCG	Serum pregnancy test
A	A wave: peak velocity flow in late diastole caused by contraction
AE	Adverse event
CFR	Code of Federal Regulations
CONSORT	Consolidated standards of reporting trials
CRF/eCRF	Case report form/electronic CRF
CS	Cardiogenic shock
DBP	Diastolic blood pressure
ECG	Electrocardiogram
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HF/AHF	Heart failure/acute heart failure
HIPAA	Health Insurance Portability and Accountability Act
E	E wave: peak velocity blood flow from LV relaxation in early diastole
E/Ea	Mitral Doppler inflow E velocity to annular tissue Doppler Ea wave velocity
ERO	Effective regurgitant orifice
eGFR	Glomerular filtration rate
ICF	Informed consent form
ICH	International Conference on Harmonisation
ICU	Intensive care unit
IEC	Independent ethics committee
IRB	Institutional review board
IND	Investigational new drug
ITT	Intent-to-Treat
IWRS	Interactive web response system
LV	Left ventricular

Abbreviation	Description
MAP	Mean arterial pressure
NDA	New drug application
PAP	Pulmonary artery pressure
P_{aw}	Mean airway pressure
PI	Principal Investigator
PK	Pharmacokinetics
SAE	Serious adverse event
SBP	Systolic blood pressure
SIV	Site initiation visit
TAPSE	Tricuspid annular plane systolic excursion
UP	Unanticipated problem
US	United States
WHF	Worsening heart failure

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 tolerability in the 02-CL-2001a study of Lyophilized Lucinactant in adults with COVID-19 infection. 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.

1.1 Background

COVID-19 is the 3rd serious coronavirus outbreak since 2002. At this time, the mortality rate associated with COVID-19 is 5-6%. This is somewhat lower than the 10% and 36% fatality rates seen during the SARS and MERS coronavirus outbreaks respectively. The characterization of COVID-19 is rapidly evolving. Recently, transmission of COVID-19 has been confirmed from asymptomatic individuals. This may indicate that more people than expected have been infected and thus lower the overall mortality rate associated with infection. However, serious consequences exist for infected individuals with pneumonia. COVID-19 has some similarity to SARS including that it may be able to use the ACE2 receptor in the lung. However, the reported spread of infection appears to be more rapid with COVID-19 compared to SARS (2,085,769 cases in 4 months for COVID-19 vs 8098 cases in 8 months for SARS). Most reported cases have been in adults and most hospitalized patients have pneumonia. Many patients develop an ARDS-like clinical presentation, some develop a secondary infection, and many require intensive care for respiratory support including mechanical ventilation and extracorporeal membrane oxygenation (ECMO). The fatality rate for COVID-19 patients hospitalized with pneumonia is 7-10% (from CDC June 20, 2020).

COVID-19 uses the SARS-coronavirus receptor, angiotensin-converting enzyme 2 (ACE2) for entry into the host cells. ACE2 is a surface molecule highly expressed in AT2 cells of lung, along with esophageal upper epithelial cells and absorptive enterocytes from ileum and colon which indicated digestive system along with respiratory systems is a potential route for COVID-19 infection (1). AT2 cells are the cells that produce surfactant in the lung. It stands to reason that if they are damaged by COVID-19, that surfactant production would be impaired. Recent publications suggest that lung fibrosis and severe interstitial changes occur in COVID-19 patients who developed ALI/ARDS. These changes resemble those seen in premature infants who are initially ventilated due to RDS and later develop BPD, which also presents with similar lung interstitial and fibrotic changes (2,3,4). These observations may support the of use of exogenous surfactant in the treatment of ALI/ARDS caused by COVID-19.

1.1.1 Unmet Medical Need in Treatment of COVID-19 Associated ARDS

Currently, when patients' breathing deteriorates, they are placed on a mechanical ventilator (MV) to help them breathe while they are symptomatic. However, MV cannot correct the underlying issue involved with breathing difficulties, known as acute respiratory distress syndrome (ARDS), and in many cases cannot prevent death.

ARDS is a sudden, progressive pulmonary disorder characterized by lung inflammation and non-cardiogenic pulmonary edema in association with refractory hypoxemia, decreased lung compliance, and diffuse pulmonary infiltrates on the chest radiograph (5). It may occur as a direct result of injury to the lung such as with gastric content aspiration, pneumonia (both bacterial and viral), toxin inhalation or it may be associated with a wide variety of systemic processes such as sepsis, non-thoracic trauma, acute pancreatitis, multiple blood transfusions, fat embolism or shock (6). The pathophysiology of ARDS involves injury to the alveolar-capillary barrier, atelectasis, intrapulmonary shunting of blood flow and surfactant dysfunction. Despite advances in medical management in intensive care units, mortality from ARDS can be as high as 40%, and current therapy remains entirely supportive with no therapies having been demonstrated safe and efficacious and receive regulatory approval (7,8,9,10,11,12,13).

The primary goal of ARDS treatment is to identify and correct the underlying etiology. For coronavirus this is supportive care until the virus is cleared by the immune system. Prevention of potential adverse effects of mechanical ventilation such as barotrauma and volutrauma is also critical. Using mechanical ventilatory support as safely as possible and improving lung compliance can contribute to avoiding these complications.

There is an unmet medical need for a therapy that will improve the patients' respiratory status and potentially reduce the time on mechanical ventilators.

1.1.2 Lucinactant

Since the initial report of ARDS by Ashbaugh et al. (14), abnormalities of the surfactant system have been recognized. In subsequent studies, Petty and colleagues reported both qualitative and quantitative alterations in surfactant obtained from patients with ARDS (15,16). It is now widely accepted that surfactant abnormalities play a major role in the pathophysiology of ARDS, favoring alveolar collapse, ventilation/perfusion mismatch, and increased pulmonary shunt fraction (17,18,19,20). Not only have these chemical and functional changes been described in patients with established ARDS, but similar alterations have been described in patients at-risk to develop ARDS (20,21).

Degradation of native surfactant by inflammatory mediators and reactive oxygen species, and inhibition of surfactant functional activity plasma proteins have been implicated in impairment of alveolar surfactant. One of the hallmarks of ARDS is damaged alveoli and airways that are filled with fluid containing inflammatory cells, protein, inflammatory mediators and other debris. In addition, damage to the epithelial type II cells may result in decreased production and/or release of altered surfactant.

The biophysical change in the surfactant system that occurs with ARDS is an increase in minimum surface tension (20), while the biochemical changes in the surfactant system that occur with ARDS include:

1) a decrease in the total phospholipid content (20),
2) an alteration in the phospholipid profile as demonstrated by a decrease in the percentage of phosphotidylcholine (PC), dipalmitoyl phosphotidylcholine (DPPC), and phosphatidylglyerol (PG) (17,18,19,20),
3) an alteration in the fatty acid composition of the phospholipids (17,22),
4) a reduction in large surfactant aggregates (23,24), and
5) a decrease in the surfactant associated proteins SP-A, SP-B, and SP-D (20,21,23).

Since many of the major pulmonary consequences of ARDS may be directly influenced by surfactant dysfunction, replacement treatment with exogenous surfactant is potentially efficacious in this disorder. In addition, damaged alveoli and airways are filled with fluid containing inflammatory cells, protein, inflammatory mediators and other debris.

In a series of *in vitro* studies, liquid lucinactant for intratracheal instillation (SURFAXIN®) has been shown to be more resistant than natural lung surfactant and exogenous, commercially available animal-derived surfactant to the inhibitory effects of plasma proteins (including fibrinogen (25,26)), and inactivation by hypochlorous acid and reactive oxygen species (27). This is especially relevant in the milieu of the inflamed lung that leads to natural surfactant inactivation and degradation.

Additionally, lucinactant has been shown to modulate the inflammatory response in various models of lung injury. In addition to studies in a murine H1N1 influenza model, we have also generated data showing that lucinactant administration significantly attenuates protein leak and neutrophil migration into the alveolar space in a hyperoxic and LPS lung injury model in mice (28), decreases cytokine levels (including IL-6 and IL-8) in a preterm mechanically ventilated lamb model of RDS (as well in airway cell culture systems) (29), and ameliorates lung injury in a hydrochloric acid ALI model in spontaneously breathing pigs when delivered both as an intratracheal liquid instillate or as an aerosol (30,31).

1.2 Objectives

This study is designed to investigate the safety and efficacy of lyophilized lucinactant in adults 18-75 (inclusive). Efficacy and safety will be based on clinical evaluations. The primary objective is to evaluate the safety and feasibility of lucinactant SRT in treating COVID-19, as assessed by oxygenation index (OI) through 12 hours post initiation of dosing and other physiological and outcome measurements through 24 hours or through Day 30.

In addition, this study will assess other measures of efficacy to ensure consistency of results across multiple endpoints. The efficacy estimate will be used to calculate the sample size for future studies. The study also ensures that administration of lucinactant does not lead to safety concerns.

1.2.1 Efficacy Objective

The primary estimand for this study is the change from baseline in OI through 12 hours post initiation of dosing in the modified intent-to-treat (mITT) population (all randomized subjects that received study medication). In addition, this study will assess other physiological and outcome measurements through 24 hours or through Day 30. All efficacy and safety parameters will be evaluated using summary statistics. Details on the implementation of the different strategies are provided in Section 4.

1.2.2 Primary Endpoints

The primary endpoints for this study are safety and tolerability of reconstituted lyophilized lucinactant given as a bolus to patients with COVID-19 and change from baseline in OI at 12 hours post initiation of dosing. OI is defined as $P_{aw} \times FiO_2 \times 100/PaO_2$. Improvements in oxygenation should be an indicator of surfactant physiological activity on gas exchange and compliance that should underly improvement in clinical parameters.

Subject will continue to be followed for all efficacy evaluations until the time the subject completes the study or withdraws.

1.2.3 Secondary Endpoints

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

- Change from baseline through 24 hours post dosing initiation:
  - FiO_2;
  - PaO_2;

- SpO_2;
- OI;
- $PaCO_2$;
- $ETCO_2$;
- P/F and or S/F ratios, defined as PaO_2 or SpO_2 divided by FiO_2;
- Plateau pressure and peak inspiratory pressure (PIP) measured on the ventilator;
- Ventilation Index (VI). VI is defined as $[RR \times (PIP - PEEP) \times PaCO_2]/1000$;
- Lung compliance;
- Pressure-volume loops if ventilator technology permits.

- Through 30 days:
  - Daily lung compliance (static) on ventilator;
  - Ventilator free days;
  - Days in the intensive care unit (ICU);
  - Days in the hospital;
  - Incidence of all-cause mortality;
  - Organ failure free days.

1.2.4 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;
2. Peri-dosing events (desaturation, bradycardia, ET reflux, hypotension)
3. AEs and serious AEs (SAEs). SAEs that are ongoing at Day 30 will be followed for an additional 30 days;
4. Air leaks as AEs of special interest;
5. Assessments of vital signs.

1.3 Hypotheses

As this is an open-label study with no comparison group, no hypotheses will be used for this study.

2 INVESTIGATIONAL PLAN

2.1 Study Population

This study population will be comprised of adults 18-75 (inclusive) who are positive for SARS-CoV-2, are exhibiting symptoms of severe COVID-19 infection, who are intubated and are receiving mechanical ventilation in a critical care environment.

The objective of the pilot safety study is to evaluate the safety and feasibility of lucinactant administration in COVID-19 patients. A small number of patients should be sufficient to provide evidence that liquid lucinactant can be safely delivered as an intratracheal bolus. A total of up to 20 study subjects will be enrolled. Approximately 20 subjects will be enrolled at approximately 10 study sites in the US, and it is anticipated that approximately 60 subjects will be screened to meet the enrollment goal (3:1 ratio of screened to enrolled).

2.1.1 Inclusion criteria

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

1. Signed and dated ICF by the subject or legally authorized representative;
2. Age 18-75 (inclusive);
3. Assay positive for SARS-CoV-2 virus, preferably by polymerase chain reaction (PCR);
4. Endotracheal intubation and MV, within 7 days of initial intubation;
5. In-dwelling arterial line;
6. P/F ratio < 300;
7. Mean blood pressure ≥ 65 mmHg, with or without vasopressor support, immediately before enrollment;
8. Bilateral infiltrates seen on frontal chest radiograph.

2.1.2 Exclusion Criteria

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

1. Life expectancy < 48 hours or do not resuscitate orders;
2. Severe lung disease (home O_2, FEV_1 < 2 liters) not likely to respond to therapy or profound hypoxemia (ie, OI ≥ 25 or P/F < 100);
3. Severe renal impairment (creatinine clearance < 30 mL/min);
4. Within the last 6 months has received, or is currently receiving, immunosuppression therapy (azothiaprine, cyclophosphamide or methotrexate) or any transplant recipient;

5. Clinically significant cardiac disease that adversely effects cardiopulmonary function:
    a. Acute coronary syndromes or active ischemic heart disease (as assessed by the PI using troponin and ECG);
    b. Cardiac ejection fraction < 40% (if known);
    c. Need for multiple-dose vasopressors to support blood pressure (single dose vasopressors, such as Levophed™ ≤ 0.1 mcg/kg/min are allowed);
    d. Cardiogenic pulmonary edema as the etiology of the current respiratory distress;
    e. Evidence of myocarditis or pericarditis;
6. Neuromuscular disease;
7. Neutropenia (ANC < 1000);
8. Active malignancy that impacts treatment decisions or life expectancy related to this trial;
9. Suspected concomitant bacterial or other viral lung infection. Bacterial infection defined as WBC > 15k and positive blood/urine/sputum culture results within 72 hours.

2.2 Study Design and Randomization

This is a multicenter, single-treatment study in adults with COVID-19, who are being cared for in a critical care environment. Preliminary data from animal and adult human studies indicate that lucinactant could benefit those with ARDS in the context of COVID-19 infection, improving oxygenation and lessening lung damage. Furthermore, lucinactant, given early in the course of the disease, could potentially decrease the need for endotracheal intubation and mechanical ventilation.

Subjects will be enrolled into the lucinactant treatment group if they meet all the screening criteria. Treatment initiation is to begin within 6 hours of randomization. Enrolled subjects will receive reconstituted lyophilized lucinactant (30 mg total TPL/mL) as a liquid at 160 ml (~80 mg TPL/kg lean body weight [~2.7 ml/kg lean body weight]). Sites from the US will participate in this study.

For this study, the study drug (lyophilized lucinactant) is being delivered in an open-label manner. No procedures to minimize bias relative to randomization or blinding will be employed.

2.2.1 Treatment Groups

Up to 20 enrolled subjects will be administered an investigational drug product, lyophilized lucinactant. Reconstituted lyophilized lucinactant (reconstituted with sterile water for injection) will be delivered as a liquid into the trachea in quarter doses.

There is only one treatment group called “Lucinactant.” In this treatment group, the subject will receive Lyophilized lucinactant 160 ml (~80 mg TPL/kg lean body weight of 30 mg/ml

suspension), and up to 3 repeat study treatments of the same dose volume may be given if criteria are met.

Enrollment should occur as soon as possible once it has been confirmed that the subject has met all inclusion criteria and has not met any exclusion criteria, within 7 days of initial intubation. Treatment initiation is to begin within 6 hours of randomization. If the subject does not tolerate one of the 40 ml quarter doses, the dosing for that dose may be terminated at that time. It is recommended that the other quarter doses remain 40 ml; however, a lower dose may be administered for the remaining aliquots at the Investigator's discretion.

2.2.2 Repeat Dosing

Up to 3 retreatment doses are allowed no sooner than 6 hours apart (from completion of previous dose). Subjects are eligible for retreatments if they remain on MV, there is no evidence of pneumothorax, the P/F ratio is under 300 (or S/F ratio is under 315, if no arterial line is present), and there are no safety concerns that would prevent retreatment (in the opinion of the investigator). Retreatments are given at the discretion of the investigator.

Retreatment should be performed in the same manner as the initial treatment.

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

The objective of this safety pilot study is to determine if lyophilized lucinactant administration is safe and tolerable, and to assess the impact on oxygenation for those patients suffering with COVID-19. As a result, no formal sample size calculation was performed. A total of 20 subjects should be sufficient to provide evidence that liquid lucinactant can be safely delivered as an intratracheal bolus.

Thus, 20 subjects (out of approximately 60 screened) will be enrolled.

2.2.4 Study Schedule

		Primary Phase Through Day 30		
Measurement/Procedure	**Screening**	**Treatment Period (Day 1)**	**Post-Treatment Period (Days 2-5)**	**Final Period (Days 6 to 30)**
Informed consent	X			
Inclusion/exclusion Criteria	X			
Demographics	X			
Medical history	X			
Physical examination	X			
Enrollment		X		
Study treatment administration		X		
Vital signs	X	X	X[2]	X
ABG (PaO_2, $PaCO_2$, pH)		X[1]	X	X
FiO_2, SpO_2, P_{aw}, $EtCO_2$		X[1]	X	X
Ventilator parameters (rate, peak and plateau pressure, lung compliance)		X[2]	X[2]	
Respiratory support parameters	X	X	X	X
Pressure volume loops		X[3]		
AEs/SAEs		X	X	X
Concomitant medications	X	X	X	X
Final Visit/Discharge				X[4]

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

[1] Time 0 (study treatment), 1, 2, 4, 8, 12, 18, 24 hours after treatment

[2] Recorded every 12 hours at 08:00 and 20:00 through Day 5.

[3] Recorded every 2 hours through 24 hours.

[4] Occurs at Day 30, withdrawal from the study, or death (whichever occurs first).

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, randomized and received study medication (modified intent-to-treat [mITT] population), received study medication regardless of randomization (safety population), and without protocol violations (per-protocol population) will be described. If more than 5% of subjects experience a treatment interruption, a population of subjects without interruptions will also be defined.

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

Demographic parameters will be summarized by treatment group and assessed qualitatively for homogeneity of treatment groups. Continuous variables (eg, age, 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.

Race categories with small numbers (frequencies of percentages of < 10%) will be combined as 'Other' for summary displays.

3.2.2 Medical History

Medical history findings will be documented during screening. And incidence of medical history findings will be summarized by treatment group using frequency and percent.

3.3 Study and Concomitant Medication

3.3.1 Compliance

Study treatments will be administered in an in-patient setting (ie, ICU) by the PI or a person approved for dosing by Windtree. Completion of drug delivery for each treatment and re-treatment will be monitored; no other compliance measurements will be employed.

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.

Lung compliance should be recorded during screening and lung compliance will be summarized as change from baseline at each time point measured using mean, SD, median, minimum, and maximum.

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 Concomitant Medication

Concomitant medications and therapies required for the general care of the subject are permitted, including remdesivir and off-label drugs. Other investigational agents or investigational medical devices should be avoided. Concomitant medications will be documented until the time the subject completes the Day 30, is discharged from the hospital, dies, or is transferred to another hospital. Dose, route, unit, frequency of administration, indication for administration, and dates of medication will be captured on the CRF.

Concomitant medications will be classified according to the World Health Organization (WHO) drug dictionary (March 2020 or later). Applicable concomitant medications (sedatives, paralytics, vasopressors, anti-coagulants, COVID-directed antiviral and anti-inflammatory therapy) will be recorded from enrollment until the final subject assessment. 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. Subjects with protocol violations will not be included in the per-protocol population.

4 EFFICACY ANALYSIS

The efficacy objective is to evaluate the safety and feasibility of lucinactant SRT in treating COVID-19, as assessed by OI (defined as $P_{aw} \times FiO_2 \times 100/PaO_2$) at 12 hours post dosing and other physiological and outcome measurements through 24 hours or through Day 30. In addition, the study will assess other measurements changing from the baseline and the ability to administer up to 3 lucinactant for inhalation repeat treatments.

4.1 Efficacy Populations

For efficacy analyses, subjects will be summarized according to their randomized treatment.

The statistical analysis of both the primary and secondary objectives will be based on all enrolled subjects. For the efficacy analysis, the primary analysis will be based on a modified intent-to-treat population (mITT). In addition, populations of all randomized subjects (ITT) and subjects with no major protocol deviations (per-protocol) will be evaluated based upon the treatment group to which they were randomized. If treatment interruptions are experienced by > 10% of subjects, a population of subjects without treatment interruptions will also be defined and analyzed.

4.1.1 Modified Intent-to-Treat Population

The modified intent-to-treat (mITT) population is the primary efficacy analysis population and is defined as all enrolled subjects who received any treatment.

4.1.2 ITT Population

The ITT population is defined as all subjects who were randomized in the study, regardless of receipt of study treatment.

4.2 Statistical Analysis

All analyses will be performed for all subjects combined and by treatment group, by baseline value, as appropriate.

All efficacy and safety parameters will be evaluated using summary statistics. For continuous (parametric) data, data will be summarized using number (n), mean, standard deviation (SD), median, 1st quartile, 3rd quartile, minimum, and maximum. For categorical (discrete) data (eg, sex, race), data will be summarized using frequency (n) and percent.

See Section 7, Statistical Technical Issues, for details on statistical methods and calculations.

4.2.1 Primary Efficacy Endpoint

The primary endpoint is the change from baseline in OI through 12 hours post dosing. OI is define as ($FiO_2 \times P_{aw} \times 100$)/$PaO_2$. OI will be summarized using mean, standard deviation (SD), median, minimum, and maximum.

4.2.2 Secondary Endpoints

The secondary efficacy is to assess other physiological and outcome measurements through 24 hours or through Day 30 to ensure consistency of results across multiple endpoints.

Through 24 hours post treatment, OI, FiO_2, PaO_2, SpO2, PaCO2, P/F and S/F ratios, change in plateau pressure and PIP measured on the ventilator, VI, and lung compliance will be summarized as change from baseline at each time point measured using mean, SD, median, minimum, and maximum.

Through 30 days post treatment, Daily lung compliance on ventilator, ventilator free days, days in the ICU, days in the hospital, organ failure free days, and all-cause mortality will be summarized as was done for the primary endpoint.

All deaths will be summarized using frequency and percent, overall and by type of death (respiratory or not respiratory) and included as part of the assessment of safety. Time to death will also be summarized using mean, standard deviation (SD), median, minimum, and maximum. Also, the deaths will be listed by subject and narratives for each death will be included. In this study, the secondary endpoint of ventilator-free days (VFD) is a mortality adjusted assessment. This issue will be dealt with in more detail in preparation for the next study.

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. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

4.4 Subgroup Analyses

Not applicable. No sub-group analyses are planned in this study.

4.5 Exploratory Analyses

Exploratory analyses may be performed based upon subject responses to treatment.

5 SAFETY ANALYSES

5.1 Safety Population

Since this is an open-lable study with only one treatment group. The safety population is defined as all subjects who received any study medication. All safety assessments will be based on this population.

Safety analyses will be summarized by all subjects combined.

5.2 Extent of Exposure

This is a multicenter, single-treatment study. All subjects will be enrolled into the lucinactant treatment group if they meet all the screening criteria. Enrolled subjects will receive reconstituted lyophilized lucinactant (30 mg total TPL/mL) as a liquid at 160 ml (~80 mg TPL/kg lean body weight) in the first dose. The number of subjects who receive a repeat dose, the number of doses received, the amount of treatment received (based on number of treatment), and the number of subjects whose study treatment is terminated early will be summarized.

5.3 Adverse Events

An adverse event (AE) is defined as any untoward medical occurrence associated with the use of an intervention, whether or not considered intervention-related. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product [21 CFR 312.32(a), ICH E6(R2)].

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 22.0 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 will not be compared between treatment groups.

5.3.1 Peri-Dosing AEs

The incidence of peri-dosing events (desaturation, bradycardia, ET reflux, hypotension, gagging/regurgitation/vomiting) will be summarized.

5.3.2 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.

5.3.3 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.

5.3.4 Serious Adverse Events

An AE or suspected adverse reaction is considered “serious” if, in the view of either the investigator or sponsor, it results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization.

All SAEs will be listed and summarized by treatment group using frequency counts and percentages. If the same SAE occurs multiple times for the same subject, the most severe occurrence will be counted. SAEs, including multiple occurrences, will also be listed, to include severity, relationship to the study drug, gender, race, and ethnic origin.

5.3.5 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.

5.4 Clinical Assessments of Safety

5.4.1 Vital Signs

Vital signs, including body temperature, blood pressure, and heart rate, will be measured every 12 (±1.0) hours until Day 5 and at Day 30. Systolic and diastolic blood pressure should be measured using either an arterial line or a manual sphygmomanometer with the patient in a supine or semi-supine position. Weight will be measured at baseline and at Day 30.

Clinically significant vital signs will also be recorded as AEs.

5.4.2 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.

5.4.3 Respiratory Support and Supplemental Oxygen

The respiratory support includs mechanical ventilation and extracorporeal membrane oxygenation (ECMO). Information on respiratory support parameters will be captured from screening through Day 30 or discharge, whichever occurs first. For each intubation and change in respiratory support, date and time, the type of respiratory support and mode, the reason for each intubation and change of respiratory support will be documented.

Lung compliance should be recorded every 12 (±1.0) hours through Day 5. The plateau pressure and peak inspiratory pressure (PIP) will be measured every 12 (±1.0) hours through Day 5. The ventilation index will be calculated.

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

5.5 Follow-Up

The follow-up period is from Day 6 to Day 30. The assessments conducted at the final visit (Day 30), including vital signs, ABG (PaO_2, $PaCO_2$, pH), FiO_2, SpO_2, P_{aw}, $EtCO_2$, Respiratory support parameters, AEs/SAEs, and Concomitant medications.

6 INTERIM ANALYSES AND DATA MONITORING

6.1 Data Monitoring Committee

The DMC, made up of at least 3 experts in the field of infectious diseases, will 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.

During the treatment and post-dosing phases, the chair of the DMC will receive regular reports on SAEs and DMC members will be periodically updated on the program and trial status. An ad hoc meeting of the DMC will occur if the chair deems it necessary to address safety in the study. The DMC may recommend that study enrollment be suspended if safety concerns are identified or suspected.

The DMC will meet after every 6 subjects have been enrolled and dosed. The DMC will continue to meet after every 6 enrollments and these reviews will continue until enrollment and dosing is complete.

The DMC review may consist of the evaluation of (1) demographics and baseline, (2) all AEs, especially peri-dosing AEs and AEs of special interest, (3) case reviews of subjects with reported SAEs, (4) summary tables of all safety endpoints, and (5) any other available relevant data.

Following a meeting, the DMC will provide timely recommendations to the Windtree study team. Recommendations may consist of, but not be limited to the following:

- Continue the study as planned
- Suspend study enrollment, pending additional information
- Close study enrollment

An independent statistician, not a member of the committee, will be responsible for the statistical analysis of the data.

6.2 Interim Analyses/DMC Meetings

No interim analyses are planned, other than the safety assessments performed by the DMC.

6.3 Data Monitoring

Clinical data (including AEs, concomitant medications, and expected adverse reactions data) will be entered into a 21 CFR Part 11-compliant data capture system. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate.

Members of Windtree's Data Management department are responsible for data processing, in accordance with procedural documentation and a study specific Data Management Plan (DMP). Windtree's Data Management will also provide eCRF Completion Guidelines; extra training will be provided to the study sites when necessary.

Clinical data will be entered directly from the source documents. 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. Corrections for an existing eCRF record will automatically be recorded by the eCRF system (audit trail capturing the time, date, and the identification of the user who entered or updated eCRF data). Recorded corrections by the eCRF will create an electronic audit trail of study documentation.

Database lock will occur once all quality assurance procedures have been completed; this will include but not be limited to the following: (1) all site-based study data have been entered into the eCRF, (2) all entered data have been reconciled and reviewed by Windtree or designee, and (3) all data related queries have been rendered and resolved.

All procedures for the handling and analysis of data will be conducted using good computing practices meeting FDA guidelines for the handling and analysis of data for clinical trials.

7 STATISTICAL TECHNICAL ISSUES

7.1 Methods of Assigning Subjects to Treatment Groups

Subjects will be enrolled into the lucinactant treatment group if they meet all the screening criteria. Enrolled subjects will receive reconstituted lyophilized lucinactant (30 mg total TPL/mL) as a liquid at 160 ml (~80 mg TPL/kg lean body weight [~2.7 ml/kg lean body weight]). Sites from the US will participate in this study.

This is a single-treatment, open-label study, so there are no randomized procedures.

7.2 Blinding/Masking

Not applicable as this is an open-lable study. No procedures to minimize bias relative to blinding will be employed.

7.3 Details on Statistical Methods

There is no comparison in the study, since the study has only one treatment group. There is no model fitted by any statistical methodology in the study.

The continuous efficacy endpoints will be summarized using mean, standard deviation (SD), median, minimum, and maximum. And the discrete efficacy endpoints will be summarized using frequency and percent.

7.4 Multiplicity

Not applicable. There is no multiple comparison in the study.

8 GENERAL ANALYSIS DEFINITIONS

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

8.1 Baseline Definition

Baseline is defined as the measurements at the start of study drug administration for subjects enrolled in the treatment.

8.2 Windows for Visits

Accurate clock times will be recorded for each timed event in military time (24-hour clock). Day 1 is the day of enrollment; Day 2 begins at midnight following enrollment; Day 3 is the 2nd day following randomization; Day 30 will be the 29th day after the day of randomization.

All assessments at pre-specified time points are to be conducted within the windows specified in the protocol. Summary tables will use the pre-specified time points, not the actual times, to summarize the data.

8.3 Site Pooling Methods

As no statistical modeling will be performed, pooling of centers will not be done.

9 REFERENCES

1. Hoffmann M, Kleine-Weber H, Krüger N, Müller M, Drosten C, Pöhlmann S. bioRxiv. [Online].; 2020 [cited 2020 01 31. Available from: www.bioRxiv.org.
2. Bernheim A, XM, Huang M, Yang Y, Fayad ZA, Zhang N, et al. Chest CT Findings in Coranavirus Disease-19 (COVID-19): Relationship to Duration of Infection. Radiology. 2020 Feb 20.
3. Hosseiny M, Kooraki S, Gholamrezanezhad A, Reddy S, Myers L. Radiology Perspective of Coronavirus Disease 2019 (COVID-19): Lessons From Severe Acute Respiratory Syndrome and Middle East Respiratory Syndrome. AJR Am J Roentgenol. 2020 Feb;: p. 1-5.
4. Song F, Shi N, Shan F, Zhang Z, Shen J, Lu H, et al. Emerging 2019 Novel Coronavirus (2019-nCoV) Pneumonia. Radiology. 2020 Feb; 295: p. 210-217.
5. Gregory TJ, Steinberg KP, Spragg R, Gadek JE, Hyers TM, Longmore WJ, et al. Bovine surfactant therapy for patients with acute respiratory distress syndrome. Am J Respir Crit Care Med. 1997 Apr; 155(4): p. 1309-1315.
6. Bernard GR, Artigas A, Brigham KL, Carlet J, Falke K, Hudson L, et al. The American-European Consensus Conference on ARDS. Definitions, mechanisms, relevant outcomes, and clinical trial coordination. Am J Respir Crit Care Med. 1994 Mar; 49(3 Pt 1): p. 818-824.
7. Nicholas TE, Doyle IR, Bersten AD. Surfactant replacement therapy in ARDS. White knight or noise in the system? Thoax. 1997; 52: p. 195-197.
8. Brandstetter RD, Sharma KC, DellaBadia M, Cabreros LJ, Kabinoff GS. Adult respiratory distress syndrome: A disorder in need of improved outcome. Heart & Lung. 1997; 26: p. 3-14.
9. Wiedemann HP, Tai DY. Adult respiratory distress syndrome (ARDS): Current management, future directions. Cleve Clin J Med. 1997; 64: p. 365-372.
10. Fulkerson WJ, MacIntyre N, Stamler J, Crapo JD. Pathogenesis and treatment of the adult respiratory distress syndrome. Arch Intern Med. 1996; 156: p. 29-38.
11. Schuster DP, Kollef MH. Acute respiratory distress syndrome. Dis Mon. 1996 May; 42(5): p. 270-326.
12. Schuster DP, Kollef MH. The acute respiratory distress syndrome. New Engl J Med. 1995; 332: p. 27-37.
13. Sachdeva RC, Guntupalli KK. Acute respiratory distress syndrome. Crit Care Clin. 1997; 13: p. 503-521.
14. Ashbaugh DG, Bigelow DB, Petty TL, Levine BE. Acute respiratory distress in adults. Lancet. 1967; 2: p. 319-323.
15. Petty TL, Reiss OK, Paul GW, Silvers GW, Elkins ND. Characteristics of pulmonary surfactant in adult respiratory distress syndrome associated with trauma and shock. Am Rev Respir Dis. 1977 Mar; 115(3): p. 531-536.

16. Petty TL, Silvers GW, Paul GW, Stanford RE. Abnormalities in lung elastic properties and surfactant function in adult respiratory distress syndrome. Chest. 1979 May; 75(5): p. 571-574.
17. Hallman M, Spragg RG, Harrell JH, Moser KM, Gluck L. Evidence of lung surfactant abnormality in respiratory failure: Study of bronchoalveolar lavage phospholipids, surface activity, phospholilpase activity, and plasma myoinositol. J Clin Invest. 1982; 70: p. 673-683.
18. Pison U, Seeger W, Buchhorn R, Joka T, Brand M, Obertacke U, et al. Surfactant abnormalities in patients with respiratory failure after multiple trauma. Am Rev Respir Dis. 1989 Oct; 140(4): p. 1033-1039.
19. Pison U, Obertacke U, Brand M, Seeger W, Joka T, Bruch J, et al. Altered pulmonary surfactant in uncomplicated and septicemia-complicated courses of acute respiratory failure. J Trauma. 1990 Jan; 30(1): p. 19-26.
20. Gregory TJ, Longmore WJ, Moxley MA, Whitsett JA, Reed CR, Fowler AA, et al. Surfactant chemical composition and biophysical activity in acute respiratory distress syndrome. J Clin Invest. 1991 Dec; 88(6): p. 1976-1981.
21. Greene KE, Wright JR, Steinberg KP, Ruzinski JT, Caldwell E, Wong WB, et al. Serial changes in surfactant-associated proteins in lung and serum before and after onset of ARDS. Am J Respir Crit Care Med. 1999 Dec; 160(6): p. 1843-1850.
22. Schmidt R, Meier U, Yabut-Perez M, Walmrath D, Grimminger F, Seeger W, et al. Alteration of fatty acid profile in different surfactant phospholipids in acute respiratory distress syndrome and severe pneumonia. Am J Respir Crit Care Med. 2001 Jan; 163(1): p. 95-100.
23. Günther A, Schmidt R, Feustel A, Meier U, Pucker C, Ermert M, et al. Surfactant subtype conversion is related to loss of surfactant apoprotein B and surface activity in large surfactant aggregates. Am J Respir Crit Care Med. 1999 Jan; 159(1): p. 244-251.
24. Veldhuizen RA, McCaig LA, Akino T, Lewis JF. Pulmonary surfactant subfractions in patients with acute respiratory distress syndrome. Am J Respir Crit Care Med. 1995 Dec; 152(6 Pt 1): p. 1867-1871.
25. Amirkhanian JD. Inhibitory effects of oxyradicals on surfactant function utilizing in vitro Fenton reaction. Lun. 1998; 176: p. 63-72.
26. Manalo E, Merritt TA, Kheiter A, Amirkhanian J, Cochrane C. Comparative Effects of Some Serum Components and Proteolytic Products of Fibrinogen on Surface Tension-Lowering Abilities of Beractant and a Synthetic Peptide Containing Surfactant KL4. Pediatr Res. 1996; 39: p. 947-952.
27. Merritt T, Amirkhanian J, Helbock H, Halliwell B, Cross C. Reduction of the surface-tension-lowering ability of surfactant after exposure to hypochlorous acid. 1993; 295(Pt 1): p. 19-22.

28. Kinniry P, Pick JSS, Jain D, Solomides C, Niven R, Segal R, et al. KL4-surfactant prevents hyperoxic and LPS-induced lung injury in mice. Pediatr Pulmonol. 2006; 41(10): p. 916-928.
29. Wolfson MR, Wu J, Hubert TL, Gregory TJ, Mazela J, Shaffer TH. Lucinactant attenuates pulmonary inflammatory response, preserves lung structure, and improves physiologic outcomes in a preterm lamb model of RDS. Pediatr Res. 2012 Oct; 72(4): p. 375-383.
30. Zimmermann AM, Roberts KD, Lampland AL, Meyers PA, Worwa CT, Plumm B, et al. Improved gas exchange and survival after KL-4 surfactant in newborn pigs with severe acute lung injury. Pediatr Pulmonol. 2010; 45(8): p. 782-788.
31. Lampland AL, Wolfson MR, Mazela J, Henderson C, Gregory TJ, Meyers P, et al. Aerosolized KL4 surfactant improves short-term survival and gas exchange in spontaneously breathing newborn pigs with hydrochloric acid-induced acute lung injury. Pediatr Pulmonol. 2014; 49(5): p. 482-489.

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