

STUDY PROTOCOL:

Revefenacin in Acute Respiratory Insufficiency in COPD
(RARICO)

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1. ABBREVIATIONS & DEFINITIONS

1.1 Abbreviations

ACT = Airway Clearance Therapy

ARF = Acute Respiratory Failure

CRF = Case Report Form

COPD = Chronic Obstructive Pulmonary Disease

C_{stat} = Static Compliance

CTSI = Clinical & Translational Science Institute

GCP = Good Clinical Practice

HIPAA = Health Insurance Portability and Accountability Act

IRB = Institutional Review Board

LAMA = long-acting muscarinic antagonist

LAR = Legally Authorized Representative

LOS = Length of Stay

FDA = Food and Drug Administration

FiO₂ = Fraction of Inspired Oxygen

ICU = Intensive Care Unit

MV = Invasive Mechanical Ventilation

MICU = Medical Intensive Care Unit

n = Number

P/F = PaO₂/FiO₂ ratio

PaCO₂ = Partial pressure of arterial carbon dioxide

PaO₂ = Partial pressure of arterial oxygen

PB-980 = Puritan BennettTM 980 ventilator

PBW = Predicted Body Weight

PC = Pressure Control Ventilation

PEEP = Positive End-Expiratory Pressure

PEEP_i = Intrinsic PEEP

PHI = Protected Health Information

PI = Principal Investigator

PIP = Peak Inspiratory Pressure

P_{res} = Plateau Pressure

PS = Pressure Support Ventilation

QA = Quality Assurance
RCT = Randomized controlled trial
RR-UCLA = Ronald Reagan UCLA Medical Center
R_{stat} = Static Resistance
RT = Respiratory Therapist
SAE = Serious Adverse Event
SAMA = Short-acting muscarinic antagonist
SIS = Study Information Sheet
SM-UCLA = Santa Monica UCLA Medical Center
UAB = Unassisted Breathing
UCLA = University of California, Los Angeles
UP = Unanticipated Problem
VC = Volume Control Ventilation
VFD = Ventilator-free Day

1.2 Definitions

Adverse Event: Any untoward medical occurrence associated with the use of a drug or a study procedure, whether or not considered drug related.

Adverse reaction: An adverse reaction means any adverse event caused by a drug. An adverse reaction are a subset of all suspected adverse reactions where there is a reason to conclude that the drug caused the event.

Assisted breathing: Any level of ventilatory support at pressures higher than the unassisted breathing thresholds.

Controlled Ventilation: Any mode with a backup rate that allows clinicians to either set tidal volume to a target or adjust pressures to target a tidal volume. Examples include volume assist control, pressure assist control, pressure regulated volume control.

Extubation: Removal of an orotracheal tube, nasotracheal tube, or unassisted breathing with a tracheostomy

Funding: Mylan Specialty L.P., Morgantown, WV 26505, USA

Home: Level of residence or health care facility where the patient was residing prior to hospital admission.

Intention to Treat (ITT): All eligible and consented patients who undergo randomization will be included in the ITT cohort for the purposes of analyzing the study outcomes.

Mechanical Ventilation (MV): Assisted invasive positive pressure ventilation delivered by a nasotracheal, orotracheal, or tracheostomy tube

Legally Authorized Representative: An individual, judicial, or other body authorized under applicable law to consent on behalf of a prospective patient to the patient's participation in the clinical study.

Mortality at hospital discharge: This includes deaths from all causes at the time of discharge from the hospital.

Study Drug: Randomly assigned Revefenacin

Study Day: The day that all inclusion criteria are met is study day one. The next day is study day two, etc.

Study hospital: Defined as the hospital where the patient was enrolled.

Serious Adverse Event: Adverse events that are serious and unexpected and have a reasonable possibility that the event was due to a study procedure

Sponsor: Theravance/Mylan

Suspected adverse reaction: any adverse event for which there is a reasonable possibility that the drug caused the adverse event. Reasonable possibility means there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction

UAB (Unassisted Breathing): Spontaneously breathing with face mask, nasal prong oxygen, room air, T-tube breathing, tracheostomy mask breathing, CPAP ≤ 5 without PS or MV assistance, the use of noninvasive ventilation solely for sleep-disordered breathing or use of a nasal high flow system.

1. PROTOCOL SUMMARY

Title: Revefenacin in Acute Respiratory Insufficiency in COPD (RARICO)

Objective: To assess feasibility and obtain preliminary data for the efficacy of nebulized revefenacin in improving the lung mechanics of COPD patients with acute respiratory failure requiring invasive mechanical ventilation (MV), in comparison to a control group receiving the short-acting muscarinic antagonist ipratropium.

Hypothesis: Revefenacin can be safely administered to COPD patients with acute respiratory failure requiring mechanical ventilation reducing the time at the bedside spent by the respiratory therapist.

Specific Aims:

1. To evaluate the safety and feasibility of administering vibrating mesh nebulizer-delivered revefenacin in COPD patients with acute respiratory failure requiring invasive mechanical ventilation.
2. To evaluate differences in resource utilization between patients receiving revefenacin and ipratropium, including time spent at the bedside by the respiratory therapist (RT) for delivery of additional rescue bronchodilators and resource utilization measures.
3. To obtain preliminary data about the effect of nebulized revefenacin on respiratory mechanics, including peak inspiratory pressure (PIP), plateau pressure (P_{plat}), dynamic resistance (R_{dyn}), static resistance (R_{stat}), compliance (C_{stat}), and intrinsic PEEP ($PEEP_i$), in comparison with nebulized ipratropium.
4. To explore the effect of nebulized revefenacin on clinical outcomes including ventilator-free days (VFDs), hospital and ICU length of stay (LOS), and mortality, in comparison with nebulized ipratropium
- 5.

Study Design:

RARICO is a pragmatic, randomized, controlled, double-blinded, multi-center trial evaluating the safety and feasibility of nebulized revefenacin in comparison to nebulized ipratropium in patients with COPD and acute respiratory failure requiring invasive mechanical ventilation.

Intervention: Nebulized revefenacin 175 mcg once daily, or nebulized ipratropium 500 mcg (every 6 hours for 7 days, or until termination of invasive mechanical ventilation, whichever occurs first). All patients will also receive as-needed nebulized albuterol as well as usual supportive care for COPD and acute respiratory failure.

Inclusion Criteria: Patients must meet all inclusion criteria:

- Adults ≥ 40 years of age
- Acute respiratory failure requiring invasive mechanical ventilation
- Documented history of COPD based on spirometric evidence of $FEV_1/FVC < 70\%$
- Smoking history ≥ 10 years (current or prior)
- Invasive mechanical ventilation for ≤ 48 hours

Exclusion Criteria:

- Invasive mechanical ventilation for > 48 hours
- Chronic invasive mechanical ventilation via tracheostomy. Patients with tracheostomy alone without chronic mechanical ventilation may be enrolled.
- Expected duration of mechanical ventilation <24 hours
- Hypersensitivity to muscarinic antagonists
- Inability to tolerate albuterol
- Lack of documented COPD history
- For patients taking short- or long-acting muscarinic antagonists (SAMAs or LAMAs) at the time of screening, inability or unwillingness to undergo the SAMA or LAMA washout period (6 hours or 24 hours, respectively) prior to initiating study drug.
- Presence of ARDS or acute congestive heart failure
- Unwillingness or inability to remain on the study drug with for the duration of the study
- Unwillingness or inability to have open-label muscarinic antagonists withheld for duration of the study
- Unwillingness or inability to utilize the Puritan-Bennett 980 (PB980) ventilator
- Pulmonary comorbidities such as pneumothorax or pneumomediastinum that, in the opinion of the investigator or clinical team, can pose a risk to subject safety or interfere with the subject's ability to complete the study procedures.
- Documented restrictive lung disease or history of interstitial lung disease
- Actual body weight exceeding 1 kg per centimeter of height
- Pregnancy
- AST or ALT > 3 times the upper limit of normal, or other clinically significant acute or chronic liver disease
- Known history of glaucoma
- Enrollment in other interventional clinical trial
- Moribund patient not expected to survive >24 hours
- Decision to withhold life-sustaining treatment, except in those patients committed to full support except cardiopulmonary resuscitation
- Inability to obtain informed consent from patient or legally authorized representative (LAR)

Outcomes:**Feasibility Outcomes:**

- Respiratory therapist time utilization as reflected in the total time spent delivering the nebulizers (Revefenacin + Albuterol PRN in study group or Ipratropium + Albuterol PRN in control group) in the 10-minute increments
- Total number of delivered rescue albuterol nebulizers per study-day
- Compliance with the protocol of Revefenacin administration per study Protocol
- Frequency and number of total adverse reactions of the study drugs

Safety Outcomes:

- Paradoxical bronchospasm following study drug administration, manifested by any of the following: increased wheezing, or increase in intrinsic PEEP that in the opinion of the investigator could be attributed to the study drug
- Hypersensitivity reaction to the study drug
- New cardiac arrhythmia not explained by other reasons
- Severe urinary retention not explained by other reasons
- Severe constipation not explained by other reasons

Exploratory and Efficacy Outcomes:

- Reduction in total inspiratory resistance across the airways and ventilator circuit measured by the change in dynamic parameters derived from the respirator (Static Resistance (R_{stat}), Dynamic Resistance (R_{dyn}), Peak pressure (PIP), Resistive pressure (P_{res}) and Static compliance (C_{stat})) at the time of drug trough
- Change in dynamic parameters derived from the respirator (Static Resistance (R_{stat}), Dynamic Resistance (R_{dyn}), Peak pressure (PIP), Resistive pressure (P_{res}), Static compliance (C_{stat}), Exhaled Minute Ventilation (VE_{TOT}), P_{plat} , Intrinsic PEEP ($PEEP_i$), I:E time, End expiratory flow (EEF) rate) at the drug-peak and drug-trough on Day 1, 2, 3 and 7 of the study
- PaCO₂ and blood gas analysis
- Ventilator-free days to day 28
- ICU Length of stay
- Hospital Length of stay
- Mortality
- Ventilator compliance analysis (ventilator dyssynchrony, pressure-volume curve analysis, expiratory flow curve analysis)

2. KEY STUDY PERSONNEL

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Safety Monitoring Board: Scott Hu, MD, MSCR, Assistant Professor
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3. STUDY RATIONALE

3.1 Background

Patients with COPD are often hospitalized with acute respiratory failure. The burden is reflected in high mortality, poor quality of life, progressive lung function decline, and enormous health care costs. Acute respiratory failure requiring invasive mechanical ventilation (MV) is one of the most severe consequences of COPD. Supportive care for these patients includes the use of systemic steroids, bronchodilators and airway clearance therapy (ACT) for pulmonary toileting.

While long-acting muscarinic antagonists (LAMAs) are routinely administered to patients with COPD, little is known about their role or potential benefit in COPD patients who acutely require MV. Such patients are known to benefit from the short-acting muscarinic antagonist (SAMA) ipratropium, suggesting a role for muscarinic antagonism in the management of acute respiratory failure in this cohort. Additionally, the ability to administer LAMAs to patients receiving MV has previously been limited due to their lack of availability in nebulized form, which is more readily administered through ventilator circuits. Revefenacin (trade name YUPELRI ®) is the first FDA-approved nebulized ultra-LAMA dosed once daily [1-3]. Given its function as a long-acting bronchodilator that is practical to administer through a ventilator circuit, revefenacin may have the potential to improve lung mechanics and decrease the duration of mechanical ventilation in COPD patients with acute respiratory failure. Given its long-acting nature, revefenacin may also have the potential to improve resource utilization, specifically the need for respiratory therapists (RTs) to administer additional ancillary treatments such as nebulized albuterol and ACT.

The intensive care units at Ronald Reagan-UCLA Medical Center (RRMC) and Santa Monica UCLA Hospital (SMH) are equipped with state-of-the-art mechanical ventilators including the Puritan Bennett™ 980. This ventilator is capable of interfacing with external data systems and has the ability to track 89 respiratory parameters and events for 72 hours. The digital communication board provides multiple USB ports for connections to external drives and an HDMI output port that can be used to project the ventilator touch screen externally. Parameters such as tidal volumes, minute ventilation, peak inspiratory pressures, inspiratory time, measures of lung compliance as well as events such as changes in ventilator settings can be continuously captured, exported in digital format, and analyzed in detail. Using these technologies to capture and analyze lung-ventilator interactions, and the effect of therapies such as bronchodilators in intubated patients represents a novel approach in the respiratory research of mechanically ventilated patients.

There is a need to learn more about the use of LAMAs in hospitalized, mechanically ventilated COPD patients. We propose to prospectively evaluate such patients admitted to the intensive care units of both RRMC and SMH and compare the effects of administration of nebulized revefenacin once daily with the effects of regularly scheduled short acting ipratropium. This pilot study is

intended to evaluate the feasibility of administering this new drug in mechanically ventilated patients and obtain preliminary data about the efficacy potential of Revefenacin use in mechanically ventilated patients with acute respiratory failure in COPD. We will assess both traditional outcome measures (ventilator-free days, ICU and hospital LOS, mortality) as well as novel outcome variables evaluating respiratory mechanics (R_{stat} , PIP, P_{plat} , C_{stat} , PEEP_i , $p\text{CO}_2$).

3.2 Study Objective

The objective of RARICO is to assess the safety and feasibility of nebulized revefenacin in improving the respiratory mechanics of COPD patients with acute respiratory failure requiring MV, in comparison to a control group receiving the short-acting muscarinic antagonist ipratropium. We hypothesize that revefenacin use will be safe and feasible alternative to the use of ipratropium. In addition, we will obtain preliminary data about the efficacy of Revefenacin in comparison to ipratropium in improving the lung mechanics of COPD patients with acute respiratory failure.

3.3 Specific Aims

1. To evaluate the safety and feasibility of administering vibrating mesh nebulizer-delivered revefenacin in COPD patients with acute respiratory failure requiring invasive mechanical ventilation.
2. To evaluate differences in resource utilization between patients receiving revefenacin and ipratropium, including time spent at the bedside by the respiratory therapist (RT) for delivery of additional rescue bronchodilators and resource utilization measures.
3. To obtain preliminary data about the effect of nebulized revefenacin on respiratory mechanics, including peak inspiratory pressure (PIP), plateau pressure (P_{plat}), dynamic resistance (R_{dyn}), static resistance (R_{stat}), compliance (C_{stat}), and intrinsic PEEP (PEEP_i), in comparison with nebulized ipratropium.
4. To explore the effect of nebulized revefenacin on clinical outcomes including ventilator-free days (VFDs), hospital and ICU length of stay (LOS), and mortality, in comparison with nebulized ipratropium

5. STUDY POPULATION

5.1 Inclusion criteria

Patients must meet all inclusion criteria:

- Adults ≥ 40 years of age
- Acute respiratory failure requiring invasive mechanical ventilation
- Documented history of COPD based on spirometric evidence of FEV1/FVC $<70\%$
- Smoking history ≥ 10 years (current or prior)
- Invasive mechanical ventilation for ≤ 48 hours

5.1 Exclusion criteria

- Invasive mechanical ventilation for > 48 hours
- Chronic invasive mechanical ventilation via tracheostomy. Patients with tracheostomy alone WITHOUT chronic mechanical ventilation may be enrolled.
- Expected duration of mechanical ventilation <24 hours
- Hypersensitivity to muscarinic antagonists
- Lack of documented COPD history
- For patients taking short- or long-acting muscarinic antagonists (SAMAs or LAMAs) at the time of screening, inability or unwillingness to undergo the SAMA or LAMA washout period (6 hours or 24 hours, respectively) prior to initiating study drug.
- Presence of ARDS or acute congestive heart failure
- Unwillingness or inability to remain on the study drug with for the duration of the study
- Unwillingness or inability to have open-label muscarinic antagonists withheld for duration of the study
- Unwillingness or inability to utilize the Puritan-Bennett 980 (PB980) ventilator
- Pulmonary comorbidities such as pneumothorax or pneumomediastinum that, in the opinion of the investigator or clinical team, can pose a risk to subject safety or interfere with the subject's ability to complete the study procedures.
- Documented restrictive lung disease or history of interstitial lung disease
- Actual body weight exceeding 1 kg per centimeter of height
- Pregnancy

- AST or ALT > 3 times the upper limit of normal, or other clinically significant acute or chronic liver disease
- Known history of glaucoma
- Enrollment in other interventional clinical trial
- Moribund patient not expected to survive >24 hours
- Decision to withhold life-sustaining treatment, except in those patients committed to full support except cardiopulmonary resuscitation
- Inability to obtain informed consent from patient or legally authorized representative (LAR)

5. STUDY DESIGN

5.1 Randomized Control Trial

RARICO is a pragmatic, prospective, randomized, double-blinded, controlled, multi-center pilot study aimed to assess the safety and feasibility of Revefenacin in patients with COPD and acute respiratory failure requiring invasive mechanical ventilation, and to compare nebulized revefenacin to nebulized ipratropium use in this population. See *Figure 1* for Study diagram

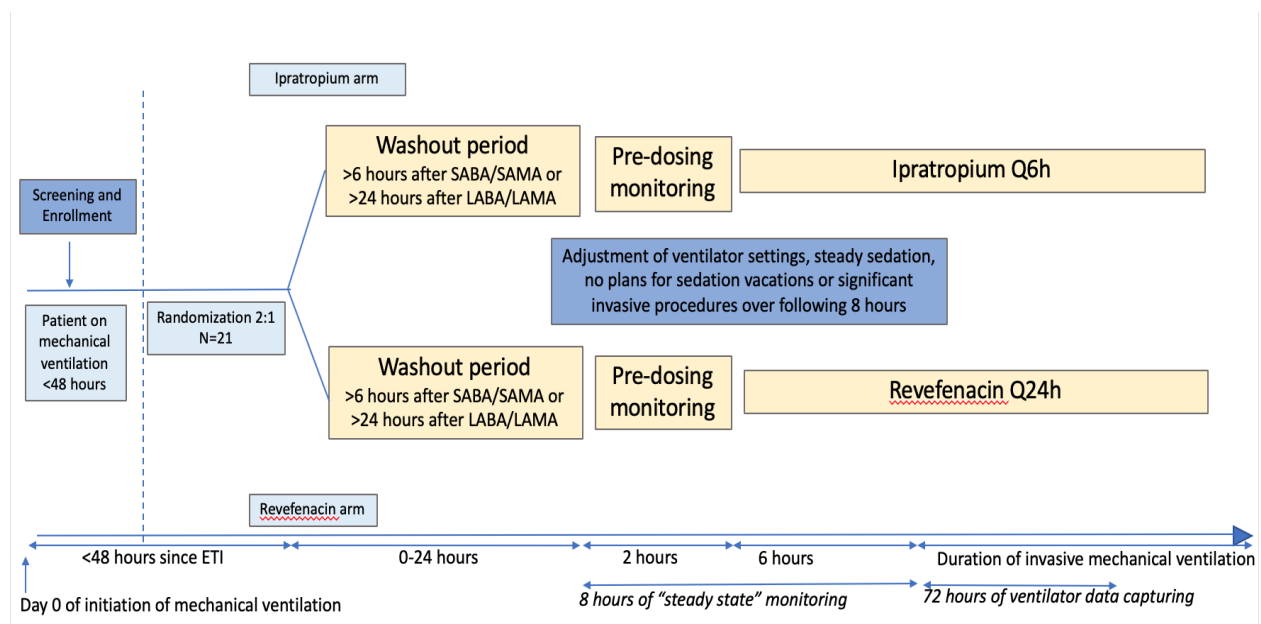


Figure 1: Study diagram

5.2 Duration

The study will recruit patients for 12 months.

5.3 Intervention

Nebulized revefenacin 175 mcg once daily, or nebulized ipratropium 500 mcg every 6 hours, for 7 days or until termination of invasive mechanical ventilation, whichever occurs first. All patients will also receive as-needed nebulized albuterol as well as usual supportive care for COPD and acute respiratory failure.

5.4 Target enrollment

Given the feasibility and safety nature of the study, the target enrollment was chosen based on convenience, rather than on a statistical power analysis. 21 subjects with 14 subjects enrolled into the revefenacin arm and 7 subjects enrolled into the ipratropium arm

5.5 Outcomes

The main focus of the study is evaluation of the safety and feasibility of Revefenacin in COPD patients with acute respiratory failure on MV, which will be assessed by the measurement of the adherence to the protocol-defined frequency of nebulized therapy with the study drug, frequency and number of total adverse effects and total respiratory therapist time spent in the delivery of nebulizers per study-day. Exploratory outcomes which can reflect airway resistive changes as a consequence of bronchodilator effects, and/or reflect improved lung mechanics and lung-ventilator interactions will also be evaluated. We will compare these outcomes between the revefenacin and ipratropium arm and will evaluate these measures for each study subject by comparing pre-drug values to drug peak (2 hours after morning dosing) and drug trough (24th hour of revefenacin dosing and 6th hour of ipratropium dosing, both coming at the same time at the end of each study day). In addition, we will analyze the differences in these outcomes at Day 1, 2, 3 and 7 and will evaluate their variability analyzing data captured over 15 minutes of continuous monitoring.

Feasibility Outcomes:

- Respiratory therapist time utilization as reflected in the total time spent delivering the nebulizers (Revefenacin + Albuterol PRN in study group or Ipratropium + Albuterol PRN in control group) in the 10-minute increments
- Total number of delivered rescue albuterol nebulizers per study-day
- Compliance with the protocol of Revefenacin administration per study Protocol
- Frequency and number of total adverse reactions of the study drugs

Safety Outcomes:

- Paradoxical bronchospasm following study drug administration, manifested by any of the following: increased wheezing, or increase in intrinsic PEEP that in the opinion of the investigator could be attributed to the study drug
- Hypersensitivity reaction to the study drug
- New cardiac arrhythmia not explained by other reasons
- Severe urinary retention not explained by other reasons
- Severe constipation not explained by other reasons

Exploratory and Efficacy Outcomes:

- Reduction in total inspiratory resistance across the airways and ventilator circuit measured by the change in dynamic parameters derived from the respirator (Static Resistance (R_{stat}), Dynamic Resistance (R_{dyn}), Peak pressure (PIP), Resistive pressure (P_{res}) and Static compliance (C_{stat})) at the time of drug trough
- Change in dynamic parameters derived from the respirator (Static Resistance (R_{stat}), Dynamic Resistance (R_{dyn}), Peak pressure (PIP), Resistive pressure (P_{res}), Static compliance (C_{stat}), Exhaled Minute Ventilation (VE_{TOT}), P_{plat} , Intrinsic PEEP ($PEEP_i$), I:E time, End expiratory flow (EEF) rate) at the drug-peak and drug-trough on Day 1, 2, 3 and 7 of the study
- PaCO₂ and blood gas analysis
- Ventilator-free days to day 28
- ICU Length of stay
- Hospital Length of stay
- Mortality
- Ventilator compliance analysis (ventilator dyssynchrony, pressure-volume curve analysis, expiratory flow curve analysis)

5.6 Definition of mechanical ventilation-related outcomes:

Static compliance (C_{stat}) is an estimate of the elasticity of the patient's respiratory system; it is expressed in mL/cmH₂O.

C_{stat} is computed from this equation

$$C_{\text{STAT}} = \frac{V_{\text{EXH}}}{P_{\text{PL END}} - \text{PEEP}} - C_C$$

Static resistance (R_{stat}) is the total inspiratory resistance across the artificial airway and respiratory system. It is an estimate of how restrictive the patient's airway is, based on the pressure drop at a given flow; it is expressed in cmH₂O/L/second. These values are computed during an operator-initiated inspiratory pause, in which the PSOL valves and exhalation valve are closed. R_{stat} is computed during a mandatory breath. R_{stat} is computed during a VC mandatory breath with a square waveform.

$$R_{\text{STAT}} = \frac{\left[1 + \frac{C_C}{C_{\text{STAT}}}\right] (P_{\text{PEAK}} - P_{\text{PL MID}})}{\dot{V}_{\text{PAT}}}$$

Dynamic resistance (R_{dyn}) indicates the impedance characteristics of the lungs, chest wall and conducting airways. It is expressed in cmH₂O/L/second on breath to breath basis in assisted control ventilation mode.

Peak Pressure (P_{peak} or PIP) is the maximum pressure measured during the inspiratory phase of the current mandatory or spontaneous breath and is updated at the end of each inspiration. The

ventilator displays negative P_{peak} values. The ventilator displays the most positive value of the low-pass filtered airway pressure measured during the inspiratory phase.

P_{peak} can be used to evaluate trends in the compliance and resistance of the respiratory system.

Plateau Pressure (P_{pl}) is the pressure measured in the ventilator breathing circuit at the end of an inspiratory pause maneuver. Because the pause maneuver is conducted with the ventilator breathing circuit sealed (PSOL valves and exhalation valve closed and assuming a leak-tight system), is the best estimate of the pressure in the patient's lungs. Beginning with the start of the pause maneuver, P_{pl} is displayed and updated continuously. At the end of the maneuver, along with the other pause data P_{pl} is "frozen," enabling you to view all of the data together. Pressing "UNFREEZE" causes the data to be discarded.

End expiratory pressure (PEEP) is the pressure measured at the end of the exhalation phase of the just completed breath, whether mandatory or spontaneous. The accuracy of the PEEP measurement is dependent of the engagement of expiratory muscles and active exhalation and should be measured during completely passive exhalation.

Total PEEP (PEEP_{TOT}) and *Intrinsic PEEP* (PEEP_I) are determined during an operator-initiated expiratory pause, in which the PSOL valves and exhalation valves are closed. PEEP_{TOT} is the pressure measured during the pause maneuver. It is an estimate of the total pressure at the end of exhalation, referenced to atmosphere. PEEP_I is an estimate of the pressure above the PEEP level at the end of exhalation.

I:E is the ratio of inspiratory time to expiratory time of any breath (mandatory and spontaneous), whether volume- or pressure-based. I:E is updated at the beginning of every inspiratory phase and is computed breath-to-breath (the value is not filtered). The I:E ratio is a fundamental parameter indicating whether a patient's breathing pattern is normal and is displayed according to respiratory care convention.

Exhaled tidal volume (V_{TE}) is the volume exhaled from the patient's lungs for a mandatory or spontaneous breath. It is computed by integrating the net flow over the expiratory period, then compliance- and BTPS compensating that value. The V_{TE} is computed based on a five-breath average. It is updated at the beginning of the next inspiratory phase.

V_{TE} is a basic indicator of the patient's ventilatory capacity and can be an indicator of the accuracy of the tidal volume setting for mandatory breaths.

Exhaled minute volume (VE_{TOT}) is an estimate of the sum of volumes exhaled for mandatory and spontaneous breaths over the previous one-minute interval. VE_{TOT} is BTPS- and compliance-compensated. During the first minute of operation following power-up or a change to respiratory rate (f) or tidal volume (VT) settings, VE_{TOT} is updated at the beginning of each new inspiration or at ten-second intervals, whichever comes first. The ventilator uses this formula to compute VE_{TOT} based on up to eight breaths: $\text{VE}_{\text{TOT}} = 60 \times (\text{total VT in } t \text{ seconds})/t$ where t is the time in seconds since the computation started.

After the first minute, the ventilator computes VE_{TOT} based on up to eight mandatory and spontaneous exhaled tidal volumes occurring in the past 60 seconds and updates the computation at the beginning of the next inspiration or the next ten-second interval, whichever comes first.

However, if the next inspiration occurs within 0.5 second of the last update, the computation is not updated at that time.

The VE_{TOT} computation is based on full and partial breaths that occurred during the preceding one-minute period. If the one-minute period includes a partial breath, then the interval is extended to include the entire breath, and the sum of all tidal volumes over this extended interval is normalized to one minute. For example, if eight full breaths and part of a ninth breath occur in the last minute, VE_{TOT} would be the sum of the nine full breaths normalized by this ratio:

60 : (the number of seconds in the extended interval)

If the patient stops breathing, VE_{TOT} continues to be updated every ten seconds, and automatically decrements.

End expiratory flow (EEF) rate is the rate of expiratory flow that occurs at the end of exhalation and can be used to determine whether expiratory time is adequate to prevent gas trapping and intrinsic PEEP. The end expiratory flow rate is calculated as the expiratory flow that occurs when flow integration terminates during exhalation or when a new breath is initiated.

6. STUDY ENROLLMENT AND WITHDRAWAL

6.1 Strategies for Recruitment and Retention

Subjects will be actively recruited for this study. They will be derived from sequential patients admitted to the ICU at Ronald Reagan Medical Center and ICU in Santa Monica Center at UCLA who meet criteria for the study as identified via review of the patient's data allowable through waiver of HIPAA authorization.

6.2 Procedures for Training Interventionists and Monitoring Intervention Fidelity

CTSI Research associates are UCLA undergraduate students who have received explicit and specific instructions in screening patients, enrolling patients, and communicating with the physicians certified in the bedside ultrasound examination to facilitate enrollment and completion of the study intervention and documentation. Weekly meetings of the CTSI students will occur to reinforce and retrain as necessary throughout the duration of the study. Prior to study initiation, the associates will practice identification of subjects and communication with the intervening physicians regarding the eligibility criteria, though the intervention will not actually be delivered until enrollment begins. CTSI Research associates will assist with filling out areas of the data forms for each patient that can easily be extracted by those with limited medical knowledge (i.e. body mass index, sex, age, lab values, numbers of x-rays, etc.). Additionally, data that require medical background to understand will be manually extracted from the chart by physicians trained in the protocol (i.e. vasopressor use and peak dose). The PI will have the ability to correct data entered incorrectly

6.3 Screening

Upon admission to the ICU, patients become eligible for twice-daily screening by the CTSI research associates. All intubated patients admitted to the MICU at RR-UCLA or SM-UCLA will be screened. In case that circumstances related to recent COVID-19 epidemics require non-infectious patients to be placed in other or separate intensive care units (6 ICU or neurocritical care, or 8ICU or liver ICU in RRMC, or step-down ICU in SM-UCLA), and in case nebulized therapies are accessible in non-medical ICUs, screening may be performed in these units if the permission of the nursing and unit directorship allows for it, and this screening would be performed following the same inclusion and exclusion criteria. Screening will be performed in the mornings to allow for adequate identification of patient's proxies, lab testing and adequate washout period timing, this way allowing for a timely enrollment and initiation of the study the following morning.

Patients meeting all eligibility criteria at the time of admission will be enrolled in the study. Patients not meeting eligibility criteria at the time of admission will be screened for 2 days (48 hours) from time of intubation. A form will be filled out to indicate that screening has taken place twice daily, and these forms will be kept in the study file locked in the MICU workroom.

For details obtained during the screening, please see *Appendix 1, Screening sheet*.

6.4 Assessment of Clinician Compliance with Study Procedural Intervention

All MICU patients will be screened daily unless they have been enrolled in the study or disqualified for entry into the study. The daily screening sheet completed by the CTSI Research Associates will be retained in the study folder. Patients enrolled will be maintained on a separate log. On this log, it will be noted which physician was contacted to perform the examination as well as when the exam and subject sheet were completed as evidenced by the ultrasound log and procedure note time stamp. The subjects who passed the screening but have not received examination and study enrollment will be documented with explanation of the reasons for failure to enroll.

6.5 Enrollment Encounter:

- Verify inclusion/exclusion criteria and enroll patient
- Determine time zero of study eligibility in consultation with nurses, residents, and EMR
- Provide Study Consent to patient or surrogate
- Initiate Study enrollment by notification of research coordinator and/or co-investigator physician
- Verify completion and documentation of testing within 24 hours from time zero of study eligibility
- Record demographic information, medical information (labs, medications, studies) for which research associates and study personnel are trained to abstract

Subjects who meet enrollment criteria will be presented with the study outline and be familiarized with the study protocol. Written consent will be handed to the patient's proxy (and introduced to the patient if feasible) for detailed review. In order to be enrolled in the study, liver function test (LFT) panel within 24 hours prior to the enrollment will be available. A documented negative pregnancy test will be required for all female participants of reproductive age.

Upon enrollment, all study-related data will be documented in the Case Report Form (CRF).

6.6 Consent

Study investigators will obtain consent for the participation in the study. Upon enrollment, the patient will be randomized into revefenacin or ipratropium arm and the washout period will start. The consent form can be found as an *Appendix 2*.

6.7 Randomization

The study coordinator will not be blinded for the study randomization and will help randomize the patient into revefenacin or ipratropium arm based on the lottery approach. Prior to the study initiation, 21 envelopes will be prepared. Each envelope will contain a card with the assignment to “Study Drug” vs. “Control”. There will be 14 “Study Drug” and 7 “Control” cards, thus randomization will be 2:1 for revefenacin vs. ipratropium arms. Folded cards will be placed in the envelopes which are going to be sealed and randomly marked with letters A-U corresponding to subjects 1-21. The coordinator will prepare an excel file with key to randomization and this file will be kept separately under the password protection and will be used by the same coordinator only in case one of 21 envelopes is damaged or lost during the study. Upon randomization, the study coordinator will notify the pharmacy about the patient’s study arm.

Unblinded study participants are: Main Study Coordinator and Pharmacists.

Blinded study participants are: all other study participants including the PI and all co-investigators, RTs, primary team, nursing and the patient and his/her surrogates.

6.8 Subject Withdrawal

Subjects are free to withdraw from participation in the study at any time after enrollment upon request by the subject or proxy. An investigator may terminate a study subject’s participation in the study if:

- 1) Any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that participation in the study would not be in the best interest of the subject.
- 2) The subject meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation.

7. STUDY METHODS AND TECHNOLOGY

7.1 Study Documentation

All study forms will be IRB approved. The following documents will be included:

1. The *Screening Form* will be maintained by CTSI RAP and will be updated on daily basis. This form will contain:
 - a. Identifying data of screened patients
 - b. Each screened patient will be assigned a number
 - c. A field determining whether the patient screen-passed or screen-failed
2. The *Study Enrollment Sheet* will be managed by the study coordinator and the other coinvestigators or study participants will not have access to it. It will contain:
 - a. Identifying data of enrolled patients
 - b. Unique study-assigned ID number
 - c. Randomization info
3. *Consent Form*
4. *RT Logbook* which will be kept at the bedside and will be updated by the RT providing care during the duration of the study
5. *Case Report Form* (CRF)

See *Appendix* to this protocol to see the forms above.

Digital data will be secured using the UCLA server, in the cloud-based drive (Box) while the backup of the documents will be kept in encrypted lap-top exclusively purchased for the study.

7.2 Equipment

All study subjects will be ventilated using Puritan Bennett™ 980 (Medtronic, Boulder, CO) mechanical ventilators.

The ICUs at RPMC and SMH are equipped with PB 980 ventilators which include Trending Software. Each ventilator is capable of interfacing with external data systems with the ability to track 89 respiratory parameters and events for 72 hours. Its innovative breath delivery technology includes a unique ventilator assurance feature which, in the event of certain system failures, will continue to deliver ventilatory support as close to the preset settings as feasible and thus offer a safety buffer for study participants. Its advanced synchrony tools will help the investigators and respiratory therapists set the ventilator to adapt to their patients' unique needs and help provide the appropriate level of support throughout the breath. Additionally, it will allow for a digital communication board to provide USB connections to external drives thus capturing breath-to-breath continuous data over Monitoring Visit's duration.

In order to export the data from the ventilator to the study database, additional equipment will be used:

1. USB to Serial adaptor
2. USB to Serial Converter, RS-232 Serial Device to a USB 2.0 Port
3. DB9 RS232 Serial Extension Cable
4. Laptop running Microsoft Windows 10 or higher
5. Software:
 - a. Serial console software: Teraterm software, this is open source.
<https://tssh2.osdn.jp/index.html.en>
 - b. Microsoft Excel for analysis

7.3 Washout period

Upon enrollment, washout will last 0 – 6 hours, depending on the last time of SAMA/LAMA use (see exclusion criteria if LAMA is used). Patients previously receiving LABA will have the LABA held for 24 hours prior to study drug initiation. Patients previously receiving SABA will have the SABA held for 6 hours prior to study drug initiation.

7.4 Evaluation of Mechanical Ventilation parameters (Monitoring Visits)

After completion of the washout period, preferably during the morning (6AM-12PM), the patient will undergo 15 minutes of respiratory data collection. In order to facilitate accurate measurement of respiratory variables, data capture will occur while the patient has a RASS score of -2 or less, and in the opinion of the investigator, is passively breathing on the ventilator.

Prior to the collection of respiratory variables, the patient will be placed on Volume Control ventilation, with a tidal volume of 8 ml/kg PBW, flow rate of 50 L/min with decelerating waveform, and PEEP 5 cm H₂O. If considered appropriate, respiratory toilet and endotracheal

suctioning will be performed. Based on an inspiratory pause maneuver and plateau pressure measurement, the tidal volume will be decreased in increments of 20ml until the plateau pressure ≤ 25 cm H₂O is reached and decreased to tidal volumes as low as 6 ml/kg PBW if needed. This adjustments of the tidal volume will be performed only during the first Monitoring Visit; all subsequent monitoring visits should maintain the same volume as the initial testing if possible.

The patient will be assessed to ensure adequate synchrony with the ventilator. The respiratory therapist will ensure that the patient is tolerating the ventilatory settings and is:

1. Compliant with ventilatory settings with RR <120% of set rate
2. Has an I:E ratio 1:2.5 or longer to secure for a full exhalation
3. The inspiratory waveform is not suggestive of an active effort
4. The expiratory flow-time waveform shows complete cessation of expiratory flow and shows no evidence of significant dynamic hyperinflation

If significant ventilator dyssynchrony is noted, bolus doses of short-acting sedative agents may be used. If sedation is not sufficient, the following ventilatory settings can be adjusted: respiratory rate (to maintain I:E ratio 2.5-4 or flow rate between 45-75L/min)

Once the subject is considered adequately sedated, hemodynamically stable with steady ventilatory support, the data capturing lap top computer will be connected to the ventilator.

Prior to the initiation of continuous data capturing, inspiratory pauses (auto mode) will be performed 3 times and expiratory pause will be performed once. These maneuvers will be completed on a square waveform flow which will allow for the measurement of PIP, P_{plat} , R_{dyn} , R_{stat} and C_{stat} , and will be repeated on decelerating waveform flow which will allow for the measurement of PIP, P_{plat} , R_{dyn} . Each of the measurements will be documented.

After the inspiratory and expiratory maneuvers are completed and obtained values documented, RT will proceed with 10 minutes of continuous ventilator data capturing which will be digitally exported and stored in the database.

In order to allow for this transition, if further ventilatory adjustments are needed to ensure compliance, inspiratory flow rate may be decreased, nevertheless, such change should be noted and applied for all future measurements. An expiratory pause (auto mode) will be performed once and PEEP_i will be collected. Upon completion of these maneuvers, the patient will then be placed on the most tolerable volume control settings as defined in the second paragraph of this section. After total of 10 minutes of uninterrupted data capturing, the previous ventilator settings will be resumed, and ongoing ventilator management will be at the discretion of the clinical team.

7.5 Monitoring Schedule

Continuous, 10-minute monitoring (estimated additional 5 minutes prior to the monitoring, required for the performance of inspiratory and expiratory hold maneuvers in addition to 10 minutes of uninterrupted data capturing) will be repeated up to 9 times during the study. Data capture will occur at time zero – before the delivery of any drug and after the washout period has

been completed. It will then be repeated at 2 hours (drug peak) and 23.5 hours (drug trough) on study days 1, 2, 3 and 7, as long as the patient remains on invasive mechanical ventilation. Each time data capture is performed, the sedation and mechanical ventilation will be adjusted as described in 7.4.

7.6 Pharmacy procedures

Drugs will be dispensed per Pharmacy protocol and pharmacist will not be blinded for patients' randomization. Prior to the beginning enrollment, the pharmacy will prepare 21 study kits labeled with letters A-U. These kits will be distributed between both study centers and will contain either the study drug + normal saline or the control drug. Each dose of potential 28 doses which would be delivered over 7 days will be numerically marked as #1, #2, etc. to minimize the confusion at the time of drug dispensing. Thus, the study arm kit will have revefenacin as #1, then normal saline left as #2, #3 and #4.

In order to enable full blinding by investigators and respiratory therapists, drugs will be dispensed in 10cc syringes and the volume of 3ml. This volume represents a standard volume of revefenacin and, in case of ipratropium (package 2.5ml), 0.5ml of normal saline will be added to the total volume of 3ml, while in case of placebo, 3ml of normal saline will be prepared. The drugs will be dispensed in light-protected sleeve and will be intended for immediate use. In order to prevent the use of medications not directly delivered by the research pharmacy, no ipratropium or revefenacin will be available in Pixus.

7.7 Drug administration

After the MV Evaluation Visit #1, study subject will be given the first dose of study drug. The drug will be delivered by the pharmacy in a form that allows coinvestigators, RTs, nursing and study subjects to remain blinded as defined in 6.7 and 7.6. It will remain a priority for the study team to minimize the time from the pickup from the pharmacy to the time of administration of the drug as per pharmacy protocol. The time of the first dose of medication will be documented as time zero. After the delivery of the first dose of the drug, the administration of study drug will continue every 6 hours. In case of revefenacin arm, this will represent the use of revefenacin at time zero, and then every 24 hours for up to 7 days. To ensure full blinding, at hours 6, 12 and 18, the subject in this arm of the study will receive placebo (normal saline). In the control arm, the subject will receive ipratropium at time zero and then every 6 hours up to 7 days.

The drug delivery visits of the respiratory therapists will be documented in the RT Log Book. On each study day, time 6, 12 and 18 hours will be exclusively drug delivery visits. The last daily dose (Time 24 hours), will be delivered at the end of Monitoring Visit (23.5 hours) which assesses the trough drug effect.

The drugs will be delivered via Aerogen solo nebulizer (Aerogen Global, Galway, Ireland). The Aerogen Solo utilizes active vibrating mesh technology. The mesh acts as a micropump drawing liquid through the holes producing a low velocity aerosol optimized for targeted drug delivery to the lungs. Vibrating mesh aerosol drug delivery systems can be used inline during any type of respiratory support including mechanical ventilation. Vibrating mesh has been demonstrated to

result in smaller aerosol particles and greater drug delivery compared to the standard jet nebulizer. The Aerogen device can deliver 9 times more aerosol dose compared to standard small volume nebulizer during mechanical ventilation.

- Estimated Treatment time – 7min
- Delivery Efficiency – 35%
- Residual Volume -0.1mL μ
- Particle Size 3.4 μ to 5.4 μ

7.8 Rescue bronchodilator use

Rescue albuterol use will be allowed to be used up to every 4 hours as needed (an order for its use “Q4h PRN” will be placed, allowing for its use as per the primary team decision and usual care management) via Aerogen nebulizers. The use of additional rescue inhalers will be documented in a RT logbook.

7.9 Collection of Respiratory Variables

Respiratory variables will be collected during:

1. Monitoring Visits. As described in 5.7, the subject will undergo up to 9 15-minute monitoring visits at times zero, and hours 2 and 23.5h of day 1, 2, 3 and 7 of the study. All data will be directly exported to the study database.
2. Prior to the completion of each of therapeutic 24h periods (morning time), respiratory therapist will capture and perform the daily ventilator summary, and this will continue until the completion of 7 days of study or the termination of invasive mechanical ventilation (extubation or death).

Complete respiratory assessment throughout the study will consist of digital data exported from the respiratory (PB 980), as well as bedside-captured data which require manual input by the RT. A respiratory logbook will be prepared for the study (*Appendix 3*). In brief, this log-book will be shared by RTs covering the patient over the course of the study and will have all study visits documented.

7.10 Data Collection

In addition to data collected from the respirator or obtained at the bedside by the RT or study team as defined in 5.9, additional data will be collected from the medical record. These data will include demographic data, medical history including detailed COPD history, labs and imaging, as well as data relevant for the hospital course – duration of hospitalization, mechanical ventilation, duration of ICU stay and other relevant outcomes including mortality. Antibiotic use, daily doses of systemic steroids, use of sedatives and analgesia, vasoactive drugs, daily net fluid balance and other clinically relevant interventions will be documented in case report form.

7.11 Lab tests and biosampling during the study:

Liver function test panel will be repeated on day 3 and day 7 if the patient remains on mechanical ventilation. Arterial blood gas (ABG) will be performed prior to the first dose and will be repeated after 2 hours and after 23.5 hours of dose delivery on day 1. Venous blood gas (VBG) will be performed prior to the first dose, and will be performed on daily basis, including day 1, 23.5 hours after the delivery of morning dose of the study drug. VBG will also be performed 2 hours after the delivery of morning dose of the drug on day 7 of the study duration in case the patient remains intubated. Additional blood gas testing will be performed as needed and at the discretion of managing team. Blood specimens for research biorepository will be collected on Day 3 (optional) of the study at the time of drug peak and trough (2 and 23.5 hours post morning dose delivery). The specimens will be collected in a red-top tube. Serum will be extracted and stored in -20°C at UCLA research facilities.

7.12 Patient care during the study

Participating patients' management of muscarinic antagonist bronchodilator will follow the study protocol. Bronchodilators will be delivered exclusively as per the Study schedule. Mechanical ventilation will be delivered only via PB980 ventilators. The mechanical ventilation strategy outside the Monitoring Visits will be at the discretion of the clinical team. Any other management will be based on the treating team's decision. Interventions which include ventilator settings changes, suctioning, patient position changes, changes in RASS will be documented in the RT logbook. Any noncompliance with the study protocol will be discouraged unless medically required and all deviations will be documented.

8. DATA EXTRACTION AND STORAGE

Data for each enrolled subject will be obtained by trained research associates and medical personnel and ultimately will be entered into a HIPAA compliant, secure database.

8.1 Data extraction

Following data will be obtained by the physical examination or extracted from patients' charts:

1. Pre-test screening (CTSI student or research coordinator) will include obtaining following data:
 - Subjects medical record number
 - Age
 - Sex
 - Patient's initials
 - Admission date and time:
 - Mechanical Ventilation Status:
 - Date of endotracheal intubation

- COPD history
 - Smoking history
2. At enrollment, prior to enrolling the patient in the study, research coordinator or co-investigator will obtain all inclusion and exclusion criteria as defined in Chapter 4 using both the medical record and the interview with the patient/surrogate. In addition, following data will be captured:
- a. APACHE II score at the time of endotracheal intubation including following labs
 - i. AaDO₂ or PaO₂ (depending on FiO₂)
 - ii. Temperature (rectal)
 - iii. Mean arterial pressure
 - iv. pH arterial
 - v. Heart rate
 - vi. Respiratory rate
 - vii. Sodium (serum)
 - viii. Potassium (serum)
 - ix. Creatinine
 - x. Hematocrit
 - xi. White blood cell count
 - xii. Glasgow Coma Scale
 - b. Additional labs which include:
 - i. Liver function panel
 - ii. Pregnancy test
 - iii. Arterial and Venous blood gas
 - c. Pulmonary function test results
 - d. Detailed COPD history including:
 - i. History of moderate or severe COPD exacerbations in the past 12 months. Moderate exacerbations are defined by the treatment in an ambulatory setting with systemic antibiotics and/or systemic glucocorticosteroids) while *severe* are the exacerbations requiring hospital admission.
 - ii. History of asthma
 - iii. Comorbidities
 - iv. History of home O₂ use
 - v. Medication history use focused on COPD drugs
 - e. History of present illness:
 - i. Presence of pneumonia
 - ii. Antibiotic use
 - iii. History of arrhythmia
 - f. Historical modified Medical Research Council (mMRC) questionnaire and COPD assessment tool (CAT) score prior to the hospital admission
 - g. Physical exam stressing at following:
 - Current blood pressure and heart rate
 - Vasopressor drips
 - Respiratory status with documentation of oxygenation and/or ventilation support
 - Central venous pressure
 - Any other relevant objective findings

- h. CT chest or – when not available – CXR results
3. Respiratory data collection will continue throughout the duration of the study as defined in 7.4. Digitally exported data will directly be transferred to the CRF. Key data will include:
- a. P_{peak}
 - b. P_{plat}
 - c. C_{stat}
 - d. R_{stat}
 - e. $PEEP_i$
 - f. pCO_2

In addition, additional measures which will be extracted from the ventilator or medical chart may include:

- a. Asynchrony analysis
 - b. Pressure-volume curve analysis
 - c. Total expiratory time analysis
 - d. Minute ventilation
 - e. Expiratory flow curve analysis
4. Additional respiratory data will be obtained and documented in the RT Log Book
- f. Total time spent delivering the nebulizer drugs in 10-minute increments. RT monitoring time will not be included here
 - g. Total number of short acting beta agonists (albuterol) administered based on “as needed” request by the care-providing team
5. Upon completion of the study protocol, study patients will be followed and their outcomes will be captured:
- a. Ventilator-free days
 - b. Duration of mechanical ventilation
 - c. Length of ICU stay
 - d. Length of hospital stay
 - e. New home oxygen requirement at the discharge
 - f. Survival to discharge

8.2 Data storage:

The data will be stored in two ways:

- The obtained data will first be entered manually into the RT Log Book and CRF which will be stored in specialized protected study folders and kept locked.
- Digitally exported data will be stored in the secured encrypted database. These data will be

processed upon the termination of the study.

All data will be stored in the secured study database. The full access to the data will be granted only to the PI and the study team members involved in data analysis.

Data to be used for the study purposes will be obtained only from the hospital admission during which a subject is enrolled in the study. As hospital records are sometimes not finalized for weeks after discharge, incomplete records will be followed for completion in order to obtain all data, and the data collection period may last up to 30 days. The data obtained in digital form will be re-analyzed by blinded analysis and exported to the database in the processed form as desired outcomes.

8.3 Data Handling and Record keeping

The investigators are responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data

8.4 Data Management Responsibilities

Data collection and accurate documentation are the responsibility of the study staff under the supervision of the investigator. All source documents and laboratory reports must be reviewed by the study team and data entry staff, who will ensure that they are accurate and complete.

Unanticipated problems and adverse events must be reviewed by the investigator or designee.

8.5 Data Capture Methods

As described previously, data will be collected on data sheets designed to match the online secure database and stored in a locked cabinet in the MICU inside the study folder. Once data are entered into the database, the data forms will be kept in a locked cabinet in the study folder until the completion of the study after which they will be moved by the PI to a locked cabinet outside the MICU for at least three years after study completion.

8.6 Study Records Retention

Study records will be maintained according to state and institutional guidelines from the date of study conclusion.

8.7 Protocol Deviations

A protocol deviation is any noncompliance with the clinical study protocol, or Good Clinical Practices. The noncompliance may be on the part of the subject, the investigator, or study staff. As a result of deviations, corrective actions are to be developed by the study staff and implemented promptly.

All deviations from the protocol must be addressed in study subject source documents and promptly reported to the local IRB, according to their requirements.

8.8 Source documents and access to source data/documents

UCLA will maintain appropriate medical and research records for this study and allow regulatory agencies to examine (and when required by applicable law, to copy) research records for the purposes of quality assurance reviews, audits, and evaluation of the study safety, progress and data validity.

9. STATISTICAL ANALYSIS

9.1 Data analysis

The full access to the data will be granted only to the PI and the study team members involved in data analysis. Collaborators and the Sponsor will have insight in deidentified data upon request.

Data analysis will be conducted with the help of UCLA Department of Medicine Statistics Core. External collaborators may have access only to de-identified saved ventilator-extracted data. The code for de-identified data will be known to PI and co-investigators.

This study is a pilot study exploring feasibility and safety of revefenacin use in acute respiratory failure in individuals with COPD. It is not powered to determine clinical efficacy benefit in comparison to ipratropium in this population of patient. Mean changes from baseline in each continuous measure, such as Static Resistance (R_{stat}), Dynamic Resistance (R_{dyn}) or Peak pressure (PIP) will be compared between groups over time using the mixed effects linear regression model taking into account that observations within the same subject over time are not independent. Alternatively, the above assessments could be performed under a joint modeling framework to account for potentially informative missing data due to early mortality or adverse events requiring discontinuation of the active study medication. In cases in which the outcome measures are not normally distributed we will investigate the use of data transformations (ex. log transformation). Dichotomous outcomes (ex. in hospital mortality) will be compared between groups using chi-squared tests (or Fisher's exact tests for rare events), whereas continuous measures such as ventilator free days will be compared between groups using the t-test or Wilcoxon rank sum test as appropriate. Additional analyses will involve the construction of linear or logistic regression models (depending on whether the outcomes are continuous or dichotomous) to adjust for the effect of clinical and demographic covariates such as age and comorbidity. These models will

also utilize data transformations as needed to normalize the residual distributions. A secondary analysis will utilize time to event models to compare length of stay between groups. This analysis will use Cox-Proportional Hazards regression or equivalent nonparametric models with terms for group as well as subject level covariates. Tests of significance will be two-tailed with an alpha threshold of 0.05 to designate statistical significance.

Sample size

As this is a pilot study it will be primarily used to demonstrate feasibility (compliance with study protocol of administering the drugs, RT time and total adverse effects) and to obtain preliminary data for efficacy potential. Our proposed sample size of 21 subjects is in accordance with the accepted guidelines for pilot studies in allowing us to obtain precise estimates of the specified feasibility outcomes.

We hypothesize that the time per day for administering the experimental drug is smaller than that of the control drug. Per prior data it is assumed that the time per day for administering the control drug is about 50 minutes on average (SD = 10) and that of the experimental drug is 10 minutes on average (SD = 10). With our proposed sample size of 21 patients we can estimate the above mean times to within a 95% confidence interval of ± 5.8 minutes for the experimental drug and ± 6.7 for the control drug. We will also have $>95\%$ power to show that the mean time administering the experimental drug is smaller in comparison to that of the control drug at a significance level of 0.05. Assuming that the protocol compliance rate of administering the experimental drug is about 93% (13/14) the proposed sample size of 14 patients receiving this drug will allow us to estimate this rate to within a 95 CI of 80% - 100%. Assuming that 1/14 of patients will not be able to tolerate the experimental drug due to serious adverse events our proposed sample size of 14 patients receiving this drug allows us to estimate the above rate with a 95% CI of 0-20%.

9.2 Interim Analysis

There will be no planned interim analysis during the period of active recruitment to the study

9.3 Final Analysis Plan and publication preparation

Study team retains the right to analyze and present data, and there will be no veto rights offered to external collaborators or the Sponsor of the study. Upon request, deidentified data will be shared with the Sponsor and collaborators, nevertheless, the study team should remain able to present the results of the study in the most objective form avoiding all biases that may come from external collaborators by the team's independence in final data interpretation and presentation.

10. RISK ASSESSMENT, SAFETY AND ADVERSE EFFECTS

10.1 Safety of Revefenacin and Adverse Effects

Revefenacin inhalation solution has been approved for use in a jet nebulizer specifically for the maintenance treatment of patients with chronic obstructive pulmonary disease (COPD). Data concerning its safety and tolerability have been obtained from previously published safety and efficacy studies. [1-4].

In terms of side effects, there were no differences in laboratory chemistry, hematology, or EKG data observed across treatment groups. The incidences of adverse events (AEs) and serious AEs were similar among treatment groups across both studies (Table 3 and 4, Manufacturer's data): Similar frequency of AEs were reported in all treatment groups. AEs occurring with a frequency of $\geq 2.0\%$ and higher in combined revefenacin groups in comparison to placebo include cough, nasopharyngitis, upper respiratory tract infections, and headache. (The adverse reactions reported in the long-term safety study are consistent with the AEs reported in the placebo-controlled 12-week studies.)

Other AE defined as events with an incidence of $\geq 1.0\%$, less than 2.0% , and more common than with placebo included the following: hypertension, dizziness, oropharyngeal pain and bronchitis (YUPELRI 2019). The proportion of subjects who discontinued treatment due to adverse reactions was 13% for the revefenacin-treated subjects and 19% for placebo-treated patients (YUPERLI 2019).

The incidences of AEs and serious AEs were similar between treatment groups and placebo

AEs with Revefenacin $\geq 2\%$ Incidence and Higher than Placebo (YUPERLI 2019)

SOC Preferred Terms	Revefenacin 175 mcg (N = 395) % (n)	Placebo (N = 418) % (n)
Respiratory, Thoracic and Mediastinal Disorders		
Cough	4 (17)	4 (17)
Infections and Infestations		
Nasopharyngitis	4 (15)	2 (9)
Upper respiratory tract infection	3 (11)	2 (9)
Nervous System Disorders		
Headache	4 (16)	3 (11)
Musculoskeletal and Connective Tissue Disorders		
Back pain	2 (9)	3 (1)

SAE Occurring in ≥ 2 Patients (Data on file)

Safety parameters	Revefenacin 175 mcg (N = 395) % (n)	Placebo (N = 418) % (n)
Reported at least 1 SAE	3.8 (15)	5.0 (21)
COPD	1.3 (5)	1.4 (6)
Chest pain	0.3 (1)	0
Cellulitis	0	0.2 (1)
Acute respiratory failure	0	0

Table 1: Adverse effect of revefenacin (FDA approval, YUPELRI insert)

10.2 Contraindications to Revefenacin use

Revefenacin is contraindicated in patients with hypersensitivity to revefenacin or any component of this product. Revefenacin has not been approved for the treatment of COPD exacerbations or as rescue therapy for the treatment of acute episodes of bronchospasm. Acute symptoms should be treated with an inhaled short-acting beta2-agonist. As with other inhaled medicines, revefenacin can produce paradoxical bronchospasm that may be life-threatening. If paradoxical bronchospasm occurs following dosing with Revefenacin, it should be treated immediately with an inhaled, short-acting bronchodilator. Revefenacin should be discontinued immediately and alternative therapy should be instituted. Revefenacin should be used with caution in patients with narrow-angle glaucoma. Patients should be instructed to immediately consult their healthcare provider if they develop any signs and symptoms of acute narrow-angle glaucoma, including eye pain or discomfort, blurred vision, visual halos or colored images in association with red eyes from conjunctival congestion and corneal edema. Worsening of urinary retention may occur. Use with caution in patients with prostatic hyperplasia or bladder-neck obstruction and instruct patients to contact a healthcare provider immediately if symptoms occur. Immediate hypersensitivity reactions may occur after administration of revefenacin. If a reaction occurs, revefenacin should be stopped at once and alternative treatments considered. The most common adverse reactions occurring in clinical trials at an incidence greater than or equal to 2% in the revefenacin group, and higher than placebo, included cough, nasopharyngitis, upper respiratory infection, headache and back pain. Coadministration of anticholinergic medicines or OATP1B1 and OATP1B3 inhibitors with YUPELRI is not recommended. Revefenacin is not recommended in patients with any degree of hepatic impairment.

10.3 Risk of other study drugs

The use of ipratropium has been a standard of care and its dosing in the study has been conservative. Its side effects are well described [5-9].

More common: Bladder pain, bloody or cloudy urine, cough producing mucus, difficult, burning, or painful urination, difficulty with breathing, frequent urge to urinate, lower back or side pain, shortness of breath, tightness in the chest, wheezing

Less common: Body aches or pain, chills, cough, ear congestion, fever, headache, loss of voice, runny nose, sneezing, sore throat, unusual tiredness or weakness

Rare: Constipation (continuing) or lower abdominal pain or bloating, fainting, fast, pounding, or irregular heartbeat or pulse, severe eye pain, skin rash or hives, swelling of the face, lips, or eyelids

Nebulized normal saline has only minor and spontaneously resolved adverse effects from the use of nebulized hypertonic saline. Lung function with its use is not affected [10]. Nebulized saline can therefore be used as a placebo in bronchodilator studies involving COPD patients, but it cannot be used as a placebo in trials assessing symptom relief.

Nebulized albuterol will be delivered as needed and as per primary team's decision. Its use has been a standard of care and dosing PRN regimen will allow for more frequent use if considered needed. Common side effects of albuterol include: Tremor, Increased blood pressure, Nervousness in children aged 2-6 years, Insomnia in children aged 6-12 years receiving 4-12 mg every 12 hours, Nausea, Fever, Bronchospasm, Vomiting, Headache, Dizziness, Cough, Allergic reactions. Contraindications include hypersensitivity to albuterol or severe hypersensitivity to milk proteins

10.4 Risk of other study interventions

During Monitoring Visits, patients During monitoring visits, patients may require increased sedation over their baseline. Sedation level will be determined by Richmond Agitation Sedation Scale[11], *Table 2*. The sedation, if needed, will be targeted to allow for full compliance with the ventilator, targeting RASS of -2 or less as per the investigator team's discretion. Possible side-effects of short increase in sedatives, such as hypotension, will be managed by the investigator and clinical team as per usual care.

Aside from drug interventions, the patients will undergo usual care except during the Monitoring Visits.

The Richmond Agitation–Sedation Scale

Score	Term	Description
+4	Combative	Overtly combative or violent; immediate danger to staff
+3	Very agitated	Pulls on or removes tube(s) or catheter(s) or has aggressive behavior toward staff
+2	Agitated	Frequent nonpurposeful movement or patient–ventilator dyssynchrony
+1	Restless	Anxious or apprehensive but movements not aggressive or vigorous
0	Alert and calm	Spontaneously pays attention to caregiver
-1	Drowsy	Not fully alert, but has sustained (more than 10 seconds) awakening, with eye contact, to voice
-2	Light sedation	Briefly (less than 10 seconds) awakens with eye contact to voice
-3	Moderate sedation	Any movement (but no eye contact) to voice
-4	Deep sedation	No response to voice, but any movement to physical stimulation
-5	Unarousable	No response to voice or physical stimulation

Table 2: Richmond Agitation Sedation Scale (RASS)

10.5 Risk of Death

Mortality among patients in acute respiratory failure with COPD who require mechanical ventilation is high[12]. This study targets this vulnerable population of patients understanding their tenuous clinical condition. The intervention in this study – application of a new bronchodilator which has not been previously tested in mechanically ventilated patients - is considered to be clinically relevant without the expectation of any significant risks in view of the fact that patients requiring mechanical ventilation for acute respiratory failure due to COPD have routinely been treated as part of the standard of care with nebulized short-acting bronchodilators administered with much greater frequency (four or more times per day) than the long-acting bronchodilator (once-daily revefenacin) that will be evaluated in this study.

Episodes of mechanical ventilation Monitoring will be performed using lung protective ventilatory strategies which has demonstrated benefits in mechanical ventilation [13]. Sedative use is used as standard of care in mechanically ventilated patients.

In summary, it is our impression that the study interventions should not have significant impact on mortality of study subjects.

10.6 Minimization of risks

In order to minimize the risks related to the study participation, we:

1. Apply enrollment criteria to eliminate subjects at increased risks of complications
 - a. Avoid enrolling patients with pulmonary comorbidities such as pneumothorax or pneumomediastinum that, in the opinion of the investigator or clinical team, can pose a risk to subject safety or interfere with the subject's ability to complete the study procedures
 - b. Avoid enrolling patients with actual body weight exceeding 1 kg per centimeter of height
 - c. Avoid enrolling patients with history of glaucoma
2. Discuss the risks of study participation and clarify all study procedures prior to consenting.
3. Perform lab testing to ensure no significant liver dysfunction is present as per AST or ALT > 3 times the upper limit of normal or based on the presence of other clinically significant acute or chronic liver disease. Also will perform pregnancy testing on all female subjects within reproductive age.
4. Avoid enrolling patients who are moribund, or whose survival may be affected by the goals of care
5. Strict documentation of all respiratory interventions in the RT logbook and CRF.
6. Discontinuation of the study interventions in case of significant adverse effects as defined in Chapter 10.

10.7 Potential Benefits

Revefenacin was developed to produce long-acting bronchodilation and a high degree of lung selectivity with a once-daily dose. Bronchoprotective effects of the drug could be observed as early as 5-minutes after administration of a dose. The effects were sustained for an extended period of time and lasted up to 24 hours. Revefenacin was well-tolerated by patients and did not produce typical systemic adverse effects associated with anti-cholinergic therapies in published literature [14]. Its M3 receptor specificity may lead to improved bronchodilatory effect in comparison to Ipratropium.

11. ASSESSMENT OF SAFETY

11.1 Unanticipated Problems

The Office for Human Research Protection Program (OHRPP) considers unanticipated problems involving risks to subjects or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
- related or possibly related to participation in the research (“possibly related” means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Given that the study population has by definition severely deranged physiology and laboratory values and a high risk of death as a fundamental part of their underlying disease process, abnormal laboratory values and deaths are not considered unanticipated problems for this population. Rather, the problems that we will be tracking include:

- 1) Hypersensitivity reaction to the study drug
- 2) Paradoxical bronchospasm immediately following the administration of the drug
- 3) New cardiac arrhythmia not explained by other reasons
- 4) Severe urinary retention not explained by other reasons
- 5) Severe constipation not explained by other reasons

11.2 Adverse Events

An adverse event is any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign temporally associated with the subject’s participation in the research, whether or not considered related to the subject’s participation in the research.

11.3 Serious Adverse Events

A serious adverse event (SAE) is one that meets one or more of the following criteria:

- Results in death
- Is life-threatening (places the subject at immediate risk of death from the event as it occurred)
- Results in inpatient hospitalization or prolongation of existing hospitalization
- Results in a persistent or significant disability or incapacity

An important medical event that may not result in death, be life threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

After consultation with the OHRPP, and with the understanding that patients with shock are expected to have abnormal labs, organ dysfunction, and often death, the AEs and SAEs that we are tracking include iatrogenic pneumothorax, catheter-associated bloodstream infections, and catheter associated urinary tract infections that can occur as a result of the care of patients in shock.

11.4 Time Period and Frequency for Event Assessment and Follow-Up

Unanticipated problems will be recorded in the data collection system throughout the study.

The PI will record all reportable events with start dates occurring any time after enrollment until 7 days for non-serious AEs, and 30 days for SAEs. Events will be followed for outcome information until resolution or stabilization.

11.5 Characteristics of an Adverse Event and *Relationship to Study Intervention*

To assess relationship of an event to study intervention, the following guidelines are used:

1. Related (Possible, Probable, Definite)
 - a. The event is known to occur with the study intervention.
 - b. There is a temporal relationship between the intervention and event onset.
 - c. The event abates when the intervention is discontinued.
 - d. The event reappears upon a re-challenge with the intervention.
2. Not Related (Unlikely, Not Related)
 - e. There is no temporal relationship between the intervention and event onset.
 - f. An alternate etiology has been established

11.6 Expectedness of SAEs

The Study PI will be responsible for determining whether an SAE is expected or unexpected. An adverse event will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the intervention.

11.7 Severity of Event

The following scale will be used to grade adverse events:

3. Mild: no intervention required; no impact on activities of daily living (ADL)
4. Moderate: minimal, local, or non-invasive intervention indicated; moderate impact on ADL
5. Severe: significant symptoms requiring invasive intervention; subject seeks medical attention, needs major assistance with ADL

11.8 Unanticipated Problem Reporting to IRB

Incidents or events that meet the OHRP criteria for unanticipated problems require the creation and completion of an unanticipated problem report form. OHRP recommends that investigators include the following information when reporting an adverse event, or any other incident, experience, or outcome as an unanticipated problem to the IRB:

- appropriate identifying information for the research protocol, such as the title, investigator's name, and the IRB project number;
- a detailed description of the adverse event, incident, experience, or outcome;
- an explanation of the basis for determining that the adverse event, incident, experience, or outcome represents an unanticipated problem;
- a description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the unanticipated problem.

To satisfy the requirement for prompt reporting, unanticipated problems will be reported using the following timeline:

- Unanticipated problems that are serious adverse events will be reported to the IRB within 1 week of the investigator becoming aware of the event.
- Any other unanticipated problem will be reported to the IRB within 2 weeks of the investigator becoming aware of the problem.
- All unanticipated problems should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and OHRP within one month of the IRB's receipt of the report of the problem from the investigator.

11.9 Reporting of Serious Adverse Event

The study clinician will complete a Serious Adverse Event Form and submit via fax or email within the following timelines:

- Serious adverse events regardless of relationship, will be reported by fax within 72 hours of site awareness.

All SAEs will be followed until resolution or stabilization.

11.10 Halting Rules

Should any serious adverse events or repeated adverse events appear to be related to the study interventions, the PI will work with the IRB and Independent Safety Monitor Dr. Scott Hu to determine the appropriateness of halting further enrollment in the study. Dr. Hu and the PI of this study do not have a formal mentor / mentee relationship or other arrangement that would preclude objectivity.

12. STUDY OVERSIGHT

In addition to the PI's responsibility for oversight, an Independent Safety Monitor (ISM), Dr Scott Hu, will monitor the study on a quarterly basis. The ISM is independent of the study and will be available in real time to review and recommend appropriate action regarding adverse events and other safety issues.

13.ETHICS/PROTECTION OF HUMAN SUBJECTS

13.1 Ethical Standards

The investigator will ensure that this study is conducted in full conformity with the principles set forth in The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research, as drafted by the US National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (April 18, 1979) and codified in 45 CFR Part 46 and/or the ICH E6; 62 Federal Regulations 25691 (1997).

13.2 Institutional Review Board

The protocol, study information sheet(s), screening materials, and all subject materials will be submitted to the IRB for review and approval. Approval of both the protocol and the study information sheet will be obtained before any subject is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented in the study.

13.3 Selection of subjects

Federal regulations at 45 CFR 46.111(a)(3) require the equitable selection of subjects. The ICUs, and other acute care areas of participating sites will be screened to determine if any patient meets inclusion and exclusion criteria. Data that have been collected as part of the routine management of the subject will be reviewed to determine eligibility. Study exclusion criteria neither unjustly exclude classes of individuals from participation in the research nor unjustly include classes of individuals from participation in the research. Hence, the recruitment of subjects conforms to the principle of distributive justice

13.4 Justification of including vulnerable subjects

Several U.S. task forces have deemed it is permissible to include incapable subjects in research. For example, the American College of Physicians' document allows surrogates to consent to research involving incapable subjects only "if the net additional risks of participation are not substantially greater than the risks of standard treatment." Research Ethics Commission have held the view that it is permissible to include incapable subjects in research as long as there are the potential for beneficial effects and that the research presents a balance of risks and expected direct benefits *similar* to that available in the clinical setting or "if the net additional risks of participation are not substantially greater than the risks of standard treatment."

13.5 Exclusion of Special Populations

Minors, children and pregnant patients will not be included in this study as it will be conducted in a medical intensive care unit that does not care for patients <18 years of age.

13.6 Subject Confidentiality

Subject confidentiality is strictly held in trust by the investigators, study staff, and the

sponsor(s) and their agents. This confidentiality is extended to cover testing of biological samples in addition to any study information relating to subjects.

The study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor or institution.

The study monitor or other authorized representatives of the sponsor may inspect all study documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) for the study subjects. The clinical study site will permit access to such records.

14. QUALITY CONTROL AND QUALITY ASSURANCE

Prior to enrollment, the database will be beta tested by senior medical students on the study protocol as well as the PI. Any necessary changes or improvements will be made prior to study initiation. Datasheets will be designed to exactly match the data entry fields in Database.

Specific instructions for where to find the data for each field will be provided during weekly research associate training and study meetings. Example patients will have data collected from the EMR prior to the study by three independent senior medical students and by each research associate. The data will be compared for inter-rater reliability. Corrective action by study physicians will take place pro-actively and also any time data discrepancy is found by independent review of each record.

Data will be recorded onto data sheets that exactly match the entry fields for the Database.

- Research associates will fill out the data fields for which they receive training.
- Other fields will be limited to completion by senior medical students or physicians and on which they receive training.
- Each data sheet will be independently and randomly verified prior to data entry into the database by one of the personnel of the study at the physician level.
- Entry into the database will be limited to selected personnel who receive additional training on the the database system.
- Data entry managers will have enter-only capabilities. Only the PI or designee will be allowed to alter data fields after completion of a record.
- Bi-weekly, data will be reviewed by study personnel for missing data fields. These fields will be completed from the EMR and medical record by the reviewing personnel or designee.

15. PREMATURE TERMINATION OR SUSPENSION OF STUDY

This study may be suspended or prematurely terminated if there is sufficient reasonable cause. Written notification documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to the sponsoring agency (CHQI/QERM) and the MICU director at UCLA. If the study is prematurely terminated or suspended, the principal investigator will promptly inform the IRB and will provide the reason(s) for the termination or suspension.

Circumstances that may warrant termination include, but are not limited to:

- 1) Determination of unexpected, significant, or unacceptable risk to subjects.
- 2) Insufficient adherence to protocol requirements.
- 3) Data that is not sufficiently complete and/or evaluable.
- 4) Determination of futility.
- 5) Clear and convincing evidence of benefit to the intervention such that continued randomization cannot be justified.

If there is any suspicion that any of these circumstances are met, a six month interim analysis will be performed by the Data Safety Monitoring Board that consists of the biostatisticians of David Elashoff's research group and Dr. Scott Hu of the Division of Pulmonary and Critical Care. This interim analysis would seek to determine if there exist any clear uneven differences between study group outcomes or safety issues that would warrant action.

16. REFERENCES

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17. APPENDIX

Appendix 1: Screening Form

Appendix 2: Study Enrollment Sheet

Appendix 3: Consent Form

Appendix 4: RT Logbook

Appendix 5: Case Report Form (CRF)