

**Original Research****Comparison of Nebulized Long-Acting Muscarinic Antagonist Revefenacin to Ipratropium in COPD Patients With Acute Respiratory Failure Requiring Mechanical Ventilation: Results of the RARICO Study**

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***Running Head:*** Results of the RARICO Study

***Keywords:*** revefenacin; long-acting muscarinic antagonist; COPD; acute respiratory failure;  
bronchodilators; mechanical ventilation

***Abbreviations:***

***Funding Support:*** This study was supported by an investigator-initiated grant funded by  
Theravance and Viatris (formerly Mylan).

***Date of Acceptance:*** October 2, 2026 | ***Published Online Date:*** October 20, 2026

***Citation:*** Barjaktarevic I, Dartt M, Chen S, et al. Comparison of nebulized long-acting  
muscarinic antagonist revefenacin to ipratropium in COPD patients with acute respiratory failure  
requiring mechanical ventilation: results of RARICO study. *Chronic Obstr Pulm Dis*. 2026;  
Published online October 20, 2026.

<https://doi.org/10.153256/jcopdf.2026.0804>

***This article has an online supplement.***

**ABSTRACT:**

**Background:** Revefenacin is a nebulized long-acting muscarinic antagonist approved for maintenance therapy in stable chronic obstructive pulmonary disease (COPD). We conducted a pilot study to evaluate the feasibility and safety of revefenacin in mechanically ventilated COPD patients with acute respiratory failure (ARF), and compare its use with the short-acting muscarinic antagonist ipratropium, the current standard inpatient therapy.

**Methods:** In this double-blind, randomized controlled pilot study, intubated COPD patients were assigned to revefenacin 175mcg once daily plus three placebo doses, or ipratropium 500mcg via vibrating mesh nebulizer every 6 hours, for up to 7 days. The primary endpoints were safety and feasibility; exploratory endpoints included ventilator-derived respiratory mechanics and clinical outcomes.

**Results:** Twenty-one patients (mean age  $76 \pm 11$  years,  $60 \pm 51$  pack years smoking, percent-predicted FEV<sub>1</sub>  $56 \pm 26\%$ ) were randomized to revefenacin (N=12) or ipratropium (N=9). Duration of mechanical ventilation was similar between groups ( $2.5 \pm 2.3$  vs  $3.6 \pm 2.8$  days;  $P=0.83$ ), with similar number of administered doses ( $2.8 \pm 2.1$  vs  $14.2 \pm 11.1$ ;  $P=0.74$ ). Daily nebulization time was significantly lower with revefenacin ( $7.2 \pm 1.0$  vs  $26.8 \pm 5.3$  minutes;  $P<0.01$ ). Adverse events were infrequent and comparable between the groups. Revefenacin improved dynamic resistance ( $R_{dyn}$ ) post-dose ( $-0.9$  vs  $+2.6$  cmH<sub>2</sub>O/L/s;  $P<0.01$ ), without differences in peak inspiratory, resistive, or plateau pressures.

**Conclusion:** Once-daily nebulized revefenacin is a feasible and safe alternative to ipratropium in mechanically ventilated COPD patients with ARF, with reduced time spent on nebulization administration. Improvements in airway resistance suggest a potential physiologic benefit, warranting further investigation.

## INTRODUCTION:

Long-acting muscarinic antagonists (LAMA) are a cornerstone of chronic obstructive pulmonary disease (COPD) management. The only currently available Food and Drug Administration-approved once-daily nebulized LAMA is revefenacin, a long-acting bronchodilator indicated for maintenance therapy in stable COPD<sup>1,2</sup>. Despite advances in outpatient management, COPD remains a leading cause of hospitalization, accounting for approximately 700,000 admissions annually in the United States, with nearly 20% of patients readmitted within 3 months<sup>3-5</sup>. Although a range of inhaled, oral, and injectable therapies are used in the outpatient settings, LAMAs—either as monotherapy or, preferably, in combination with long-acting beta-agonists—represent a foundational step in the management of progressive disease<sup>6,7</sup>. However, during hospitalization, patients are frequently transitioned away from their home regimens and treated predominantly with short-acting bronchodilators, typically delivered via nebulization<sup>8</sup>. Unfortunately, since nebulized long-acting bronchodilators remain underutilized in inpatient settings<sup>9</sup>, the reliance on short-acting agents alone may contribute to suboptimal disease control and persistently high readmission rates observed in patients with COPD<sup>7</sup>.

While primarily indicated in the management of stable COPD, revefenacin is the only available nebulized LAMA and may represent a practical and potentially advantageous alternative to short-acting bronchodilators in hospitalized patients. A particularly relevant subgroup includes COPD patients requiring mechanical ventilation (MV), regardless of the underlying cause of acute respiratory failure (ARF). We conducted a prospective, randomized, double-blind pilot trial to evaluate the safety and feasibility of nebulized revefenacin compared with nebulized ipratropium in mechanically ventilated COPD patients with acute respiratory failure.

## METHODS:

The Revefenacin in Acute Respiratory Insufficiency in COPD (RARICO) study was conducted at UCLA between October 2020 and January 2025 as a pragmatic, single-center, double-blind, prospective randomized controlled trial approved by the Institutional Review Board (IRB#20-0129). Study procedures were designed to ensure transparent reporting in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines<sup>10</sup>.

Patients admitted to the medical intensive care units at Ronald Reagan UCLA Medical Center and UCLA Santa Monica Medical Center were pre-screened using an electronic medical record dashboard to identify individuals with COPD requiring intubation. Inclusion criteria were age  $\geq 40$  years, acute respiratory failure requiring invasive mechanical ventilation (MV), documented COPD based on prior spirometry ( $FEV_1/FVC < 70\%$ ), smoking history  $> 10$  pack-years (current or former), and duration of MV  $< 96$  hours at enrollment. Exclusion criteria included chronic respiratory failure requiring long-term MV, suspected liver disease, moderate-to-severe acute respiratory distress syndrome (ARDS;  $PaO_2/FiO_2 < 150$ ), other significant pulmonary comorbidities, or anticipated extubation within 24 hours of first dosing, *Supplemental Table 1*.

Eligible participants were enrolled after written informed consent was obtained from the patient or a legally authorized surrogate. Participants were randomized in a 2:1 ratio to receive revefenacin 175 mcg once daily (2.5 mL revefenacin plus 0.5 mL normal saline followed by three 3 mL normal saline placebo doses at 6, 12, and 18 hours to maintain blinding), or ipratropium 500 mcg (3 mL) every 6 hours. All treatments were administered via a vibrating mesh nebulizer (VMN; Aerogen™ Solo, Aerogen Global, Galway, Ireland). Short-acting beta-agonists (albuterol or levalbuterol) were permitted every 4 hours as needed at the discretion of the treating team. Before administration of the first study dose, participants underwent a 6-hour washout from short-acting bronchodilators and a 24-hour washout from long-acting bronchodilators.

Enrolled participants underwent standardized monitoring visits immediately prior to study drug administration and 90–120 minutes post-dose to assess peak effect, on study Days 1, 2, 3, and 7. During these visits, patients were required to passively breathe on the ventilator with a Richmond Agitation-Sedation Scale (RASS) score  $\leq -2$ . Ventilation was standardized using volume-control mode with tidal volume 8 mL/kg predicted body weight (PBW), inspiratory flow 50 L/min (decelerating waveform), and positive end-expiratory pressure (PEEP) of 5 cm H<sub>2</sub>O<sup>11</sup>.

If necessary, tidal volume was reduced in 20 mL increments to a minimum of 6 mL/kg PBW to achieve a plateau pressure  $\leq 25$  cm H<sub>2</sub>O (measured via inspiratory pause)<sup>12</sup>. Airway clearance, including suctioning, was performed as clinically indicated prior to data collection. Subsequent monitoring visits were conducted using the same ventilator settings. Patients were required to meet

predefined criteria for ventilator synchrony, including respiratory rate  $<120\%$  of the set rate, inspiratory-to-expiratory (I:E) ratio  $\geq 1:2.5$  to ensure complete exhalation, absence of inspiratory effort on waveform analysis, and expiratory flow consistent with full return to baseline without evidence of dynamic hyperinflation. If dyssynchrony was observed, short-acting sedatives were administered; if needed, ventilator settings were adjusted (I:E ratio 1:2.5–1:4; inspiratory flow 45–75 L/min). Once adequate sedation and synchrony were achieved, ventilator data were captured via a connected laptop. All participants were ventilated using a Puritan Bennett™ 980 ventilator (Medtronic, Boulder, CO), enabling breath-by-breath assessment of peak inspiratory pressure ( $P_{\text{peak}}$ ), plateau pressure ( $P_{\text{plat}}$ ), dynamic resistance ( $R_{\text{dyn}}$ ), static resistance ( $R_{\text{stat}}$ ), resistive pressure ( $P_{\text{res}}$ ), and intrinsic PEEP ( $\text{PEEP}_i$ ). Pre-dose, peak, and trough bronchodilator effects on respiratory mechanics were compared between the revefenacin and ipratropium groups. Before continuous data acquisition, three inspiratory pauses and one expiratory pause were performed. Respiratory mechanics were obtained using a volume-controlled mode with both constant (square) inspiratory flow waveform for consistent assessment of plateau pressures. Subsequently, 10 minutes of continuous ventilator data were captured, digitally exported, and stored in the study database. Following data collection, baseline ventilator settings were restored, and further ventilator management was left to the discretion of the clinical team.

Baseline demographic data, medical history, including the most recent spirometry, and complete hospitalization records were reviewed. Study treatment was administered for up to 7 days or until discontinuation of invasive MV, whichever occurred first (Supplemental Figure 1). The primary outcomes of this pilot study were feasibility and safety. Feasibility endpoints included respiratory therapist (RT) time utilization (including time required for rescue short-acting beta-agonist [SABA] administration), total number of rescue SABA doses, and protocol adherence. Safety endpoints included the frequency and total number of adverse events related to study treatments. Exploratory endpoints included changes in respiratory mechanics across the airway and ventilator circuit, *Supplemental Table 2*. Additional exploratory efficacy outcomes included arterial blood gas parameters (including  $\text{PaCO}_2$ ), ventilator-free days through Day 28, intensive care unit (ICU) length of stay, hospital length of stay, and mortality.

### *Statistical analysis*

This pilot study was not powered to detect differences in clinical efficacy between revefenacin and ipratropium. Dichotomous outcomes (e.g., in-hospital mortality) were compared using chi-square or Fisher's exact tests, as appropriate. Continuous variables (e.g., ventilator-free days) were compared using the Student's t-test or Wilcoxon rank-sum test, based on data distribution.

## RESULTS:

### *Demographic and clinical characteristics of the study cohort*

Of 24 patients randomized, 3 withdrew consent or clinically deteriorated prior to receiving study drug. The remaining 21 patients were included in the analysis, with 12 assigned to revefenacin and 9 to ipratropium. Participants had a mean age of  $76.2 \pm 11.2$  years, a smoking history of  $60.4 \pm 50.5$  pack-years, and a mean FEV<sub>1</sub> of  $56 \pm 26\%$  predicted. Most patients home regimens included long-acting bronchodilators (95%) and inhaled corticosteroids (81%). Over half were on supplemental home oxygen (57.1%). Comorbidities were prevalent, including chronic heart failure (52.4%) and diabetes mellitus (42.9%). Majority of patients was admitted via the emergency department (66.7%), and the most common etiologies of respiratory failure were pneumonia (43%) and COPD exacerbation (33%). Study duration ranged from 2 to 7 days, with a mean (SD) of 3.0 (2.5) days, *Table 1*.

### *Comparison of clinical characteristics between the revefenacin and ipratropium arms*

As presented in *Table 1*, Baseline characteristics were similar between groups. Mean age was  $77.4 \pm 6.8$  vs  $74.7 \pm 15.7$  years in the revefenacin and ipratropium groups, respectively, with 50.0% vs 44.4% female participants. Smoking history was higher in the revefenacin group ( $67.5 \pm 54.0$  vs  $46.7 \pm 43.7$  pack-years). Pulmonary function was comparable between groups, including post-bronchodilator percent-predicted FEV<sub>1</sub> ( $63.5 \pm 30.5\%$  vs  $46.7 \pm 18.9\%$ ), FVC ( $82.2 \pm 26.8\%$  vs  $68.6 \pm 21.9\%$ ), FEV<sub>1</sub>/FVC ratio ( $55.7 \pm 14.1\%$  vs  $52.1 \pm 14.1\%$ ), and DLCO ( $50.3 \pm 14.4\%$  vs  $51.2 \pm 16.0\%$ ). Baseline outpatient use of long-acting bronchodilators was similar, including LAMAs (100.0% vs 88.9%), inhaled corticosteroids (83.3% vs 77.8%), and LABAs (83.3% vs 88.9%). A history of asthma was less common in the revefenacin group (0% vs 33.3%), whereas obstructive sleep apnea was more frequent (58.3% vs 11.1%). Other comorbidities, including heart failure and chronic kidney disease, were comparable between groups.

*Feasibility of revefenacin use in mechanically ventilated COPD patients with ARF*

All participants completed the planned study interventions without missed doses prior to discontinuation of mechanical ventilation or completion of the 7-day study period. Following enrollment, patients remained intubated and received revefenacin or ipratropium for a similar duration ( $2.5 \pm 2.3$  vs  $3.6 \pm 2.8$  days;  $P=0.83$ ). Patients in the revefenacin group received fewer total doses of active study drug ( $2.8 \pm 2.1$  vs  $14.2 \pm 11.1$ ;  $P<0.01$ ) and required significantly less daily nebulization time ( $7.2 \pm 1.0$  vs  $26.8 \pm 5.3$  minutes;  $P<0.01$ ). Use of rescue SABA was minimal, with no doses in the revefenacin group compared with 2 doses in the ipratropium group.

*Safety of revefenacin use*

Both treatments were generally well tolerated, with no paradoxical bronchospasm or hypersensitivity reactions observed. Three adverse events (AEs) were reported. In the revefenacin group, one patient developed urinary retention, a known class effect of muscarinic antagonists<sup>13</sup>. A second event of transaminitis ( $>3 \times$  upper limit of normal) occurred in a patient with abdominal sepsis requiring surgical intervention and was deemed unrelated to study treatment. In the ipratropium group, one episode of transient tachycardia, potentially consistent with a class effect, was observed. No additional AEs or serious adverse events (SAEs) were reported, *Table 2*.

*Clinical efficacy of revefenacin*

All participants in the revefenacin group were alive at Day 28 post-intubation (100% vs 55.6% in the ipratropium group;  $P<0.01$ ), although survival at hospital discharge did not differ between groups. A greater proportion of patients in the revefenacin group were extubated by Day 28 (100% vs 77.8%;  $P=0.09$ ), with similar durations of mechanical ventilation and ICU stay, *Figure 1*. There were no between-group differences in changes in  $\text{PaO}_2$  or  $\text{PaCO}_2$  from pre-dose to peak drug effect.

*Respiratory mechanics and airway interaction with positive-pressure ventilation*

To compare pre-dose and peak post-drug respiratory mechanics, inspiratory pause maneuvers were used.  $P_{\text{pl}}$  minimally changed by  $+0.3 \pm 1.3$  vs.  $+0.1 \pm 2.5$  cmH<sub>2</sub>O in the revefenacin and ipratropium arms, respectively,  $P=0.96$ ), while  $P_{\text{res}}$  change ( $-0.7 \pm 4.8$  vs.  $+1.2 \pm 1.2$ ,  $P=0.2$ ) and  $P_{\text{peak}}$  change ( $-1.0 \pm 5.0$  vs.  $+1.3 \pm 3.1$ ,  $P=0.34$ ) demonstrated a minimal trend toward improved airway resistance in the revefenacin arm compared to the ipratropium arm, respectively. While  $R_{\text{stat}}$

changed similarly in both arms when comparing pre- and post-drug effect,  $R_{\text{dyn}}$  was significantly improved in the revefenacin compared to the ipratropium arm ( $-0.9 \pm 2.4$  vs.  $2.6 \pm 3.3$  cmH<sub>2</sub>O /L/sec,  $P < 0.01$ ), *Table 3*.

Based on the continuous monitoring of respiratory waveforms (DCI data) and ventilatory parameters, no significant differences between the two arms were observed, with similar average changes from pre-drug to post peak drug effect in peak expiratory flow ( $-1.8 \pm 2.4$  vs.  $-1 \pm 2.6$ ,  $P = 0.6$ ), end-expiratory flow rates ( $-0.5 \pm 2.1$  vs.  $0 \pm 0.4$ ,  $P = 0.6$ ) and total PEEP ( $-0.1 \pm 0.3$  vs.  $-0.1 \pm 2.7$  cmH<sub>2</sub>O,  $P = 0.6$ ) in the revefenacin vs. the ipratropium arm, respectively.

## DISCUSSION:

The RARICO study was a pragmatic pilot trial designed to evaluate the feasibility and safety of revefenacin, a nebulized LAMA, in mechanically ventilated COPD patients with acute respiratory failure. In this double-blind randomized controlled trial, revefenacin, compared with ipratropium, was feasible to administer in the critical care setting and was associated with reduced time required for nebulized drug delivery, without significant safety concerns. Trends toward improved clinical outcomes were observed but were not statistically significant.

Revefenacin, approved in 2018 for maintenance treatment of COPD, has been extensively studied in patients with stable moderate-to-severe disease, demonstrating improvements in trough FEV<sub>1</sub> with sustained bronchodilation over 24 hours<sup>2</sup>. Post hoc analyses suggest greater benefit in patients with more severe airflow limitation<sup>13</sup>. A recent prospective study in 60 hospitalized patients with COPD exacerbations compared jet nebulizer–delivered formoterol/revefenacin with albuterol/ipratropium, reporting similar efficacy and safety with fewer administered doses in the long-acting regimen<sup>14</sup>. However, critically ill patients requiring noninvasive or invasive mechanical ventilation were excluded. In our study, COPD exacerbation was not an exclusion criterion and approximately one-third of participants had an exacerbation at presentation; however, the primary objective was not to evaluate unstable COPD, but rather to assess the feasibility of revefenacin use in mechanically ventilated patients. To our knowledge, this is the first study to evaluate revefenacin in COPD patients with acute respiratory failure, suggesting it may represent a viable and practical therapeutic option in this setting.

Revefenacin demonstrated expected clinical performance. Consistent with its prolonged duration of action, it required less respiratory therapist (RT) time and no additional rescue SABA use. In the context of increasing emphasis on cost-efficient inpatient care, these findings suggest potential advantages of revefenacin in reducing treatment burden and workflow demands, with potential downstream impact on staff time and resource utilization. In short-term mechanically ventilated patients, nebulized revefenacin may offer practical advantages over inhaler-based delivery (e.g., metered-dose inhalers) by minimizing medication waste and simplifying administration. Although this study was not powered to detect superiority of revefenacin over ipratropium, several findings were encouraging. While higher 28-day survival and extubation rates in the revefenacin group should be interpreted cautiously, clinical outcomes consistently favored revefenacin numerically. The absence of rescue short-acting beta-agonist use and the observed improvement in dynamic airway resistance at peak effect further support that once-daily revefenacin provides bronchodilation at least comparable to four-times-daily ipratropium.

Revefenacin is not recommended in patients with hepatic impairment, as coadministration with OATP1B1 and OATP1B3 inhibitors may increase exposure to its active metabolite; however, there are no data suggesting intrinsic hepatotoxicity<sup>13</sup>. Although routine liver function monitoring is not required, transaminases were assessed in this study as an additional safety measure. One episode of transaminitis was observed and was attributed to severe abdominal sepsis rather than study treatment. Overall, there were no meaningful changes in liver enzymes in either group, supporting the hepatic safety of revefenacin in this critically ill population. One patient in the revefenacin group developed urinary retention, a recognized class effect of muscarinic antagonists; however, causality could not be definitively established given the complexity of critical illness. Tachycardia, another known class effect, was not observed in the revefenacin group but occurred in one patient receiving ipratropium<sup>2,14</sup>.

In addition to evaluating revefenacin as a therapeutic agent in mechanically ventilated COPD patients, this study assessed the feasibility and safety of vibrating mesh nebulizer (VMN) use within a closed ventilatory circuit. Nebulizers remain the primary modality for inhaled therapy in hospitalized COPD patients and are often perceived as preferable during exacerbations<sup>15</sup>; however, their use is largely driven by practical considerations rather than evidence of superior

efficacy. VMNs, a newer generation of nebulizers, generate aerosol independently of gas flow using a vibrating mesh, producing consistent particle sizes and minimizing drug loss. Integration of a VMN into a closed ventilator circuit may enhance aerosol delivery by minimizing residual volume and reducing circuit-related particle loss, thereby improving distal drug availability despite hygroscopic growth during humidification.

Prior studies and bench models demonstrate that VMNs achieve higher and more consistent lung deposition than standard jet nebulizers (SJNs), particularly under high-flow conditions<sup>16,17</sup>. It is therefore plausible that delivered doses of revefenacin in this study exceeded those typically achieved with SJNs in outpatient settings. Although enhanced delivery could theoretically increase systemic exposure, available data suggest that higher revefenacin doses remain well tolerated, and improved efficacy may primarily reflect more effective drug distribution<sup>18</sup>. Consistent with these observations, no significant safety concerns were identified despite the potential for increased drug delivery; however, the small sample size limits definitive conclusions.

Finally, this study explored the use of ventilator-derived metrics to assess airway physiology and pharmacologic response. Airway disease is traditionally evaluated using pulmonary function testing, while impulse oscillometry may be useful in patients unable to perform forced maneuvers; however, no widely adopted method provides continuous assessment of airway resistance during mechanical ventilation. Inherent properties of obstructed distal airways of COPD patients and changes induced by bronchodilators may be reflected in changes of peak expiratory pressures, dynamic and static airway resistance, resistive pressure and change in intrinsic PEEP values. This concept is not new – earlier studies evaluated the efficacy of meter-dose inhalers in ventilator-supported patients measuring the effect of delivered bronchodilators using airways resistance change<sup>19</sup>. *Guerin et al.* randomized 18 mechanically ventilated COPD patients to receive fenoterol-*ipratropium* via MDI versus nebulizer showing equivalently reduced total respiratory resistance using either of the assessed methods<sup>20</sup>. A key limitation of this approach is the typically short duration of mechanical ventilation in COPD. In our cohort, mean duration was 2.5 days, consistent with prior reports (median ~3 days, and ~2 days when COPD exacerbation is the primary etiology)<sup>21</sup>. Rapid progression to weaning further limits the feasibility of respiratory mechanics assessment, particularly in the presence of spontaneous breathing activity<sup>22</sup>.

To detect subtle treatment-related changes in airflow and respiratory mechanics, we used two complementary approaches: conventional inspiratory and expiratory pause maneuvers and continuous digital recording of ventilator-derived parameters during tidal breathing. The conventional method suggested a favorable effect of revefenacin compared with ipratropium, including improved dynamic resistance and numerical reductions in peak airway and resistive pressures. While the small sample size limits the power to detect differences in either method, the assessment of expiratory flow, particularly from continuous tidal-breathing data, was limited by light sedation and variability in respiratory effort. In larger, passively ventilator cohorts though, here reported continuous breath-to-breath analysis of airflow and respiratory mechanics using data generated by modern mechanical ventilators represents a promising approach for studying airway disease during mechanical ventilation.

Beyond efficacy and safety, the feasibility of inpatient revefenacin use also depends on its economic implications. Although the acquisition cost of revefenacin exceeds that of generic ipratropium, once-daily dosing could substantially reduce RT time utilization, administration-related supplies, and documentation associated with repeated nebulization. These operational savings could offset the higher acquisition cost and potentially reduce the overall cost of bronchodilator therapy.

Several limitations should be considered. As a pilot feasibility study with a small sample size, this analysis was not powered to compare efficacy between treatment groups or support generalizable conclusions. Randomization was skewed toward more ipratropium due to several drop-out patients whose randomization was not unblinded during the study duration. Clinical differences in the prevalence of asthma, OSA or PaO<sub>2</sub> levels, even though not statistically significant and while unavoidable in a double blinded randomized trial, may have introduced additional bias toward one or another study arm. Exposure to revefenacin was relatively brief, and some patients may not have achieved steady-state drug levels, reflecting the short and variable duration of mechanical ventilation in this population. Although pharmacokinetics was not assessed, peak effects for both agents were evaluated at 90–120 minutes post-dose to approximate comparable exposure windows<sup>23</sup>. While once-daily dosing may reduce RT time and treatment burden, the absence of increased rescue SABA use suggests that this reduction in treatment frequency did not compromise

bronchodilator effectiveness. The study focused on muscarinic antagonists alone, whereas combination therapy with beta-agonists is common in clinical practice; this design allowed for clearer assessment of revefenacin's safety profile and the use of rescue SABA as an endpoint. Finally, ventilator-derived respiratory mechanics were assessed without standardization of concurrent clinical interventions (e.g., airway clearance, diuretic use) and with less-than-ideal patient-ventilator synchrony, which may limit interpretation of these physiologic measurements.

This study has several notable strengths. To our knowledge, it is the first randomized clinical trial evaluating a nebulized long-acting muscarinic antagonist (LAMA) delivered via vibrating mesh nebulizer (VMN) in mechanically ventilated COPD patients with acute respiratory failure. These findings may inform future studies of long-acting bronchodilator therapy in hospitalized patients requiring mechanical ventilation. The use of ventilator-derived parameters to assess airway physiology and pharmacologic response represents a novel approach in this setting and may have value in selected clinical scenarios. Finally, this study supports the feasibility of delivering nebulized therapy within a closed ventilator circuit using VMN technology.

## CONCLUSIONS:

Once-daily revefenacin delivered via vibrating mesh nebulizer is a feasible and safe alternative to short-acting bronchodilators in mechanically ventilated COPD patients with acute respiratory failure. Its use is associated with reduced resource utilization, particularly decreased respiratory therapist time, while providing clinical outcomes comparable to four-times-daily ipratropium. Ventilator-derived respiratory mechanics suggest a potential improvement in dynamic airway resistance at peak effect with revefenacin. Although this pilot study was not powered for definitive efficacy comparisons, the consistency of physiologic and clinical signals supports revefenacin as a promising therapeutic option in the inpatient management of COPD. Larger, adequately powered studies are warranted to confirm these findings and further define its role in critically ill populations.

**Acknowledgement:** This study was supported by an investigator-initiated grant funded by Theravance and Viatris (formerly Mylan). Study conduct, data collection and analysis were performed by the study investigator team and independent from the Sponsor. The authors thank Theravance and Viatris for their support.

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Table 1. Demographics and Clinical Characteristics of the Revafenecin and Ipratropium Arms

| Characteristic                                 | Overall<br>N = 21 <sup>1</sup> | Ipratropium<br>N = 9 <sup>1</sup> | Revefenacin<br>N = 12 <sup>1</sup> | p-value <sup>2</sup> |
|------------------------------------------------|--------------------------------|-----------------------------------|------------------------------------|----------------------|
| <b>Age (Years)</b>                             | 76.2 ± 11.2                    | 74.7 ± 15.7                       | 77.4 ± 6.8                         | 0.670                |
| <b>Sex N (%)</b>                               |                                |                                   |                                    | >0.999               |
| Male                                           | 11 (52.4%)                     | 5 (55.6%)                         | 6 (50.0%)                          |                      |
| Female                                         | 10 (47.6%)                     | 4 (44.4%)                         | 6 (50.0%)                          |                      |
| <b>Patient Race N (%)</b>                      |                                |                                   |                                    | 0.536                |
| White                                          | 12 (60%)                       | 4 (44%)                           | 8 (73%)                            |                      |
| Black                                          | 6 (30%)                        | 4 (44%)                           | 2 (18%)                            |                      |
| Hawaii                                         | 2 (10%)                        | 1 (11%)                           | 1 (9.1%)                           |                      |
| Missing (n)                                    | 1                              | 0                                 | 1                                  |                      |
| <b>BMI (kg/m<sup>2</sup>)</b>                  | 25.3 ± 7.5                     | 23.7 ± 5.6                        | 26.5 ± 8.7                         | 0.522                |
| <b>Smoking Current</b>                         | 2 (11%)                        | 1 (14%)                           | 1 (9.1%)                           | >0.999               |
| <b>Smoking Prior</b>                           | 19 (90.5%)                     | 8 (88.9%)                         | 11 (91.7%)                         |                      |
| <b>Mean Pack Years</b>                         | 60.4 ± 50.5                    | 46.3 ± 43.7                       | 67.5 ± 53.9                        | 0.325                |
| <b>mMRC<sup>3</sup> N (%)</b>                  |                                |                                   |                                    | 0.460                |
| 0-1                                            | 7 (35.0%)                      | 2 (25%)                           | 5 (42%)                            |                      |
| 2                                              | 3 (15%)                        | 2 (25%)                           | 1 (8%)                             |                      |
| 3-4                                            | 10 (50%)                       | 4 (50%)                           | 6 (50%)                            |                      |
| <b>History of exacerbations N (%)</b>          |                                |                                   |                                    | >0.999               |
| 0                                              | 9 (43%)                        | 4 (44%)                           | 5 (42%)                            |                      |
| 1-2                                            | 5 (24%)                        | 2 (22%)                           | 3 (25%)                            |                      |
| 3 or more                                      | 5 (24%)                        | 2 (22%)                           | 3 (25%)                            |                      |
| <b>FEV<sub>1</sub>* (Liters) (%)</b>           | 55.6 ± 26.4                    | 46.7 ± 18.9                       | 63.5 ± 30.5                        | 0.414                |
| <b>FVC* (Liters) (%)</b>                       | 75.8 ± 24.9                    | 68.6 ± 21.9                       | 82.2 ± 26.8                        | 0.514                |
| <b>FEV<sub>1</sub>/FVC (%)</b>                 | 54.0 ± 13.8                    | 52.1 ± 14.1                       | 55.7 ± 14.1                        | 0.513                |
| <b>DLCO* Hg (ml/mmHg/min) (%)</b>              | 50.7 ± 14.7                    | 51.2 ± 16.0                       | 50.3 ± 14.4                        | >0.999               |
| <b>Current History of Asthma N (%)</b>         | 3 (14%)                        | 3 (33%)                           | 0 (0%)                             | 0.063                |
| <b>DM* N (%)</b>                               | 9 (43%)                        | 3 (33%)                           | 6 (50%)                            | 0.660                |
| <b>ESRD* on HD* N (%)</b>                      | 1 (4.8%)                       | 0 (0%)                            | 1 (8.3%)                           | >0.999               |
| <b>OSA* N (%)</b>                              | 8 (38%)                        | 1 (11%)                           | 7 (58%)                            | 0.067                |
| <b>Home O<sub>2</sub> N (%)</b>                | 12 (57%)                       | 6 (67%)                           | 6 (50%)                            | 0.660                |
| <b>SABA/SAMA N (%)</b>                         | 17 (81%)                       | 6 (67%)                           | 11 (92%)                           | 0.272                |
| <b>LABA N (%)</b>                              | 18 (86%)                       | 8 (89%)                           | 10 (83%)                           | >0.999               |
| <b>LAMA N (%)</b>                              | 20 (95%)                       | 8 (89%)                           | 12 (100%)                          | 0.429                |
| <b>ICS N (%)</b>                               | 17 (81%)                       | 7 (78%)                           | 10 (83%)                           | >0.999               |
| <b>Nebulizers used at home N (%)</b>           | 13 (62%)                       | 5 (56%)                           | 8 (67%)                            | 0.673                |
| <b>Emphysema present on imaging N (%)</b>      | 15 (71%)                       | 6 (67%)                           | 9 (75%)                            | >0.999               |
| <b>Airway wall thickening on imaging N (%)</b> | 15 (71%)                       | 6 (67%)                           | 9 (75%)                            | >0.999               |
| <b>Bronchiectasis present on imaging N (%)</b> | 7 (33%)                        | 2 (22%)                           | 5 (42%)                            | 0.642                |
| <b>Primary ARF etiology N (%)</b>              |                                |                                   |                                    |                      |
| Septic shock                                   | 2 (9.5%)                       | 0 (0%)                            | 2 (17%)                            | 0.486                |
| Cardiac arrest                                 | 2 (9.5%)                       | 2 (22%)                           | 0 (0%)                             | 0.171                |
| Pneumonia                                      | 9 (43%)                        | 3 (33%)                           | 6 (50%)                            | 0.660                |
| COPD Exacerbation                              | 7 (33%)                        | 4 (44%)                           | 3 (25%)                            | 0.397                |
| Congestive heart failure                       | 1 (4.8%)                       | 0 (0%)                            | 1 (8.3%)                           | >0.999               |
| <b>PNA* present N (%)</b>                      | 15 (71%)                       | 6 (67%)                           | 9 (75%)                            | >0.999               |
| <b>COPDE* present N (%)</b>                    | 11 (52%)                       | 5 (56%)                           | 6 (50%)                            | >0.999               |
| <b>Heart Rate (HR)</b>                         | 104.1 ± 27.3                   | 116.2 ± 28.3                      | 95.0 ± 23.6                        | 0.201                |
| <b>Mean Arterial Pressure (MAP)</b>            | 87.4 ± 18.6                    | 93.7 ± 21.0                       | 82.8 ± 15.8                        | 0.213                |
| <b>Respiratory Rate (RR)</b>                   | 21.9 ± 6.8                     | 20.3 ± 8.6                        | 23.1 ± 5.2                         | 0.617                |

| Characteristic                           | Overall<br>N = 21 <sup>1</sup> | Ipratropium<br>N = 9 <sup>1</sup> | Revefenacin<br>N = 12 <sup>1</sup> | p-value <sup>2</sup> |
|------------------------------------------|--------------------------------|-----------------------------------|------------------------------------|----------------------|
| Glasgow Coma Scale <sup>4</sup> (GCS)    | 9.0 ± 4.7                      | 8.3 ± 5.3                         | 9.4 ± 4.6                          | 0.495                |
| White Blood Cells (10E <sup>3</sup> /uL) | 12.7 ± 6.5                     | 10.4 ± 5.2                        | 14.5 ± 7.0                         | 0.177                |
| Creatinine (mg/dL)                       | 1.3 ± 1.0                      | 1.0 ± 0.4                         | 1.5 ± 1.2                          | 0.434                |
| PaO <sub>2</sub> (mmHg)                  | 130.8 ± 100.5                  | 174.3 ± 137.2                     | 99.2 ± 48.8                        | 0.160                |
| AST (SGOT) (u/L)                         | 46.0 ± 35.6                    | 55.4 ± 44.9                       | 38.9 ± 26.5                        | 0.776                |
| ALT (SPGT) (u/L)                         | 28.6 ± 19.4                    | 32.3 ± 23.9                       | 25.8 ± 15.8                        | 0.915                |
| Alkaline Phosphatase (u/L)               | 114.6 ± 66.3                   | 120.9 ± 75.8                      | 109.9 ± 61.3                       | 0.831                |
| Conjugative Bilirubin (mg/dL)            | 0.2 ± 0.2                      | 0.2 ± 0.1                         | 0.3 ± 0.2                          | 0.343                |
| Total Bilirubin (mg/dL)                  | 0.5 ± 0.3                      | 0.5 ± 0.2                         | 0.5 ± 0.3                          | 0.885                |
| Arterial pH                              | 7.4 ± 0.1                      | 7.4 ± 0.0                         | 7.5 ± 0.1                          | 0.475                |
| PaO <sub>2</sub> (mmHg)                  | 109.3 ± 75.3                   | 138.4 ± 98.9                      | 85.4 ± 39.4                        | 0.068                |
| PaCO <sub>2</sub> (mmHg)                 | 45.7 ± 13.9                    | 43.9 ± 15.0                       | 47.1 ± 13.5                        | 0.498                |
| Tidal Volume (mL)                        | 389.5 ± 63.3                   | 391.1 ± 81.0                      | 388.3 ± 50.1                       | 0.886                |
| Set respiratory rate (breaths/min)       | 19.0 ± 4.1                     | 19.3 ± 3.9                        | 18.7 ± 4.4                         | 0.692                |
| Flow (L/min), square                     | 40.7 ± 9.3                     | 42.0 ± 8.3                        | 39.8 ± 10.3                        | 0.612                |
| Flow (L/min), decelerating               | 51.7 ± 10.1                    | 55.3 ± 9.7                        | 48.6 ± 9.8                         | 0.189                |
| PEEP* (cmH <sub>2</sub> O)               | 5.2 ± 1.0                      | 5.1 ± 1.3                         | 5.3 ± 0.9                          | 0.437                |
| FiO <sub>2</sub> (%)                     | 40.0 ± 16.4                    | 34.4 ± 7.3                        | 44.2 ± 20.2                        | 0.188                |

<sup>1</sup>Mean ± SD; n (%)

<sup>2</sup>Kruskal-Wallis rank sum test; Fisher's exact test; NA

<sup>3</sup>Modified Medical Research Council (mMRC) dyspnea scale: Modified Medical Research Council (mMRC) dyspnea scale ranges from 0–4, with higher scores indicating greater severity of breathlessness

<sup>4</sup>Glasgow Coma Scale (GCS) ranges from 3–15 and is calculated as the sum of eye opening (1–4), verbal response (1–5), and motor response (1–6); higher scores indicate better neurological status

\*FEV<sub>1</sub>, forced expiratory volume in 1 second; FVC, forced vital capacity; TLC, total lung capacity; DLCO, diffusing capacity of the lung for carbon monoxide; DM, diabetes mellitus; ESRD on HD, end-stage renal disease on hemodialysis; OSA, obstructive sleep apnea; PNA, pneumonia; COPDE, chronic obstructive pulmonary disease exacerbation; PEEP, positive end-expiratory pressure

\*\*Missing data are summarized as follows: pulmonary function variables—FEV<sub>1</sub> (n=2), FVC (n=2), FEV<sub>1</sub>/FVC (n=2), TLC (n=9), DLCO (n=4); laboratory variables—bilirubin (n=9); clinical variables—BMI (n=3), smoking status (n=3), pack-years (n=3), mMRC (n=1), GCS (n=2), PaO<sub>2</sub> (n=2), flow (n=1)

Table 2. Feasibility and safety of revefenacin use compared to ipratropium in COPD patients in acute respiratory failure

| Characteristic                                                      | Overall<br>N = 21 <sup>1</sup> | Ipratropium<br>N = 9 <sup>1</sup> | Revefenacin<br>N = 12 <sup>1</sup> | p-value <sup>2</sup> |
|---------------------------------------------------------------------|--------------------------------|-----------------------------------|------------------------------------|----------------------|
| Study duration per patient, days                                    | 3.0 ± 2.5                      | 3.6 ± 2.8                         | 2.5 ± 2.3                          | 0.828                |
| Duration of mechanical ventilation after treatment initiation, days | 7.1 ± 9.4                      | 5.6 ± 6.0                         | 7.9 ± 11.1                         | 0.735                |
| Total doses given per patient                                       | 12.0 ± 10.1                    | 14.7 ± 11.6                       | 9.9 ± 8.8                          | 0.744                |
| Doses missed                                                        | 0                              | 0                                 | 0                                  |                      |
| Number of study drug doses administered                             | 7.7 ± 9.2                      | 14.2 ± 11.1                       | 2.8 ± 2.1                          | <0.001               |
| Respiratory therapist time per dose, minutes                        | 7.0 ± 1.2                      | 6.7 ± 1.3                         | 7.2 ± 1.0                          | 0.450                |
| Respiratory therapist time per day, minutes                         | 15.6 ± 10.5                    | 26.8 ± 5.3                        | 7.2 ± 1.0                          | <0.001               |
| Rescue doses                                                        | 0.1 ± 0.4                      | 0.2 ± 0.7                         | 0.0 ± 0.0                          | 0.248                |
| Total Number of Adverse Reactions during the study                  | 3 (14%)                        | 1 (11%)                           | 2 (17%)                            | >0.999               |
| AST max change                                                      | 11.0 ± 67.2                    | 1.3 ± 63.2                        | 18.3 ± 72.0                        | 0.776                |
| ALT max change                                                      | 13.6 ± 36.1                    | 12.1 ± 38.8                       | 14.7 ± 35.6                        | 0.943                |
| Paradoxical bronchospasms correct                                   | 0                              | 0                                 | 0                                  |                      |
| Hypersensitivity reaction                                           | 0                              | 0                                 | 0                                  |                      |
| New Cardiac arrhythmia                                              | 1 (4.8%)                       | 1 (11%)                           | 0 (0%)                             | 0.429                |
| Severe urinary retention                                            | 1 (5.3%)                       | 0 (0%)                            | 1 (10%)                            | >0.999               |
| Severe constipation                                                 | 0                              | 0                                 | 0                                  |                      |

<sup>1</sup>Mean ± SD; n (%)<sup>2</sup>Kruskal-Wallis rank sum test; Fisher's exact test; NA

\*Missing data are summarized as follows: duration of mechanical ventilation after treatment (n=2); severe urinary retention (n=2); severe constipation (n=2)

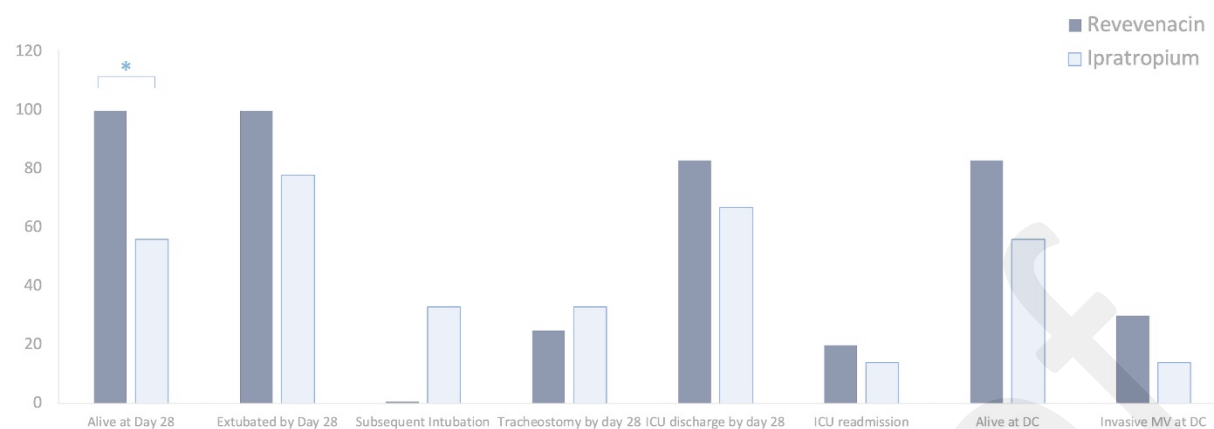
Table 3: Respiratory mechanics and airway interaction with positive-pressure ventilation

| Characteristic                                                      | Ipratropium<br>N = 9 <sup>1</sup> | Revefenacin<br>N = 12 <sup>1</sup> | p-value <sup>2</sup> |
|---------------------------------------------------------------------|-----------------------------------|------------------------------------|----------------------|
| <b>Maneuver</b>                                                     |                                   |                                    |                      |
| Peak inspiratory pressure (Ppeak), difference pre/post dose         | (-1) ± 5                          | 1.3 ± 3.1                          | 0.34                 |
| Compliance (Cstat), difference pre/post dose                        | 0.2 ± 2.3                         | (-0.8) ± 9.3                       | 0.79                 |
| Plateau pressure (Ppl), difference pre/post dose                    | (-0.3) ± 1.3                      | 0.1 ± 2.5                          | 0.96                 |
| Static resistance (Rstat), difference pre/post dose                 | 0 ± 4.6                           | (-3.1) ± 10.6                      | 0.56                 |
| Dynamic resistance (Rdyn), difference pre/post dose                 | (-0.9) ± 2.4                      | 2.6 ± 3.3                          | <0.01                |
| Resistive airway pressure (Pres), difference pre/post dose          | (-0.7) ± 4.8                      | 1.2 ± 1.2                          | 0.20                 |
| <b>DCI data (average over ≥3 min)</b>                               |                                   |                                    |                      |
| Averaged peak pressure, difference pre/post dose                    | (-0.7) ± 2.5                      | (-0.5) ± 11.9                      | 0.88                 |
| Averaged resistive airway pressure (Pres), difference pre/post dose | 0.1 ± 3.5                         | (-0.1) ± 2.1                       | 0.46                 |
| Averaged mean airway pressure (Pmean), difference pre/post dose     | 0.1 ± 0.5                         | (-0.6) ± 1.3                       | 0.36                 |
| End-inspiratory pressure, difference pre/post dose                  | (-0.2) ± 1.3                      | (-0.7) ± 2.0                       | 1.00                 |
| Averaged total expiratory volume (VeTot), difference pre/post dose  | 0.2 ± 0.6                         | (-0.2) ± 0.4                       | 0.37                 |
| Averaged total PEEP, difference pre/post dose                       | (-0.1) ± 0.3                      | (-0.1) ± 2.7                       | 0.62                 |
| Averaged dynamic compliance, difference pre/post dose               | 2.1 ± 6.1                         | (-3.2) ± 11                        | 0.37                 |
| Averaged dynamic resistance, difference pre/post dose               | 0.2 ± 1.1                         | 0.6 ± 0.8                          | 0.26                 |
| Peak expiratory flow (average), difference pre/post dose            | (-1.8) ± 2.4                      | (-1) ± 2.6                         | 0.59                 |
| End expiratory flow (average), difference pre/post dose             | (-0.5) ± 2.1                      | 0 ± 0.4                            | 0.60                 |
| Delta CO <sub>2</sub> , difference pre/post dose                    | 0 ± 6.3                           | (-0.6) ± 3.7                       | 0.41                 |
| Delta O <sub>2</sub> , difference pre/post dose                     | (-0.4) ± 22.4                     | (-11.3) ± 34.4                     | 0.49                 |
| Averaged peak pressure, difference pre/post dose                    | (-0.7) ± 2.5                      | (-0.5) ± 11.9                      | 0.88                 |
| Averaged resistive airway pressure (Pres), difference pre/post dose | 0.1 ± 3.5                         | (-0.1) ± 2.1                       | 0.46                 |

<sup>1</sup>Mean ± SD; n (%), <sup>2</sup>Kruskal-Wallis rank sum test; Fisher's exact test; NA

\*Positive value of the difference pre/post dose suggests decrease in the evaluated parameter after the drug administration

Figure 1. Clinical efficacy of revefenacin



## Online Supplement

*Supplemental Table 1: eligibility criteria***Inclusion criteria**

Adults  $\geq 40$  years of age

Acute respiratory failure requiring invasive mechanical ventilation

Documented history of COPD based on spirometry with percent predicted post bronchodilator  $FEV_1/FVC < 70\%$

Smoking history  $\geq 10$  years (current or prior)

Invasive mechanical ventilation for  $\leq 96$  hours

**Exclusion criteria**

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

Persistent 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 severe ARDS defined by  $P/F$  ratio  $< 150$  at the time of enrollment

Unwillingness or inability to remain on the study drug with for the 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.

Clinically significant diagnosed restrictive 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 narrow-angle 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)

*Supplemental Table 2: Definition of mechanical ventilation-related outcomes:*

Static compliance ( $C_{\text{stat}}$ ) is an estimate of the elasticity of the patient's respiratory system; it is expressed in mL/cmH<sub>2</sub>O.

$C_{\text{stat}}$  is computed from this equation

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

Static resistance ( $R_{\text{stat}}$ ) 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 cmH<sub>2</sub>O/L/second. These values are computed during an operator-initiated inspiratory pause, in which the PSOL valves and exhalation valve are closed.  $R_{\text{stat}}$  is computed during a mandatory breath.  $R_{\text{stat}}$  is computed during a VC mandatory breath with a square waveform.

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

Dynamic resistance ( $R_{\text{dyn}}$ ) indicates the impedance characteristics of the lungs, chest wall and conducting airways. It is expressed in cmH<sub>2</sub>O/L/second on breath to breath basis in assisted control ventilation mode.

Peak Pressure ( $P_{\text{peak}}$  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  $P_{\text{peak}}$  values. The ventilator displays the most positive value of the low-pass filtered airway pressure measured during the inspiratory phase.  $P_{\text{peak}}$  can be used to evaluate trends in the compliance and resistance of the respiratory system.

Plateau Pressure ( $P_{\text{pl}}$ ) 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.

Resistive pressure ( $P_{res}$ ) in mechanical ventilation is the pressure needed to overcome airflow resistance in the ventilator circuit, endotracheal tube, and the patient's own airways (like bronchioles), representing the difference between peak inspiratory pressure ( $P_{peak}$ ) and plateau pressure ( $P_{plat}$ )

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.

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:  $VE_{TOT} = 60 \times (\text{total VT in } t \text{ seconds})/t$  where  $t$  is the time in seconds since the computation started.

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.

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.

*Supplemental figure 1: Study consort diagram*

