

Clinical Trial Protocol	
UTMC Trial No.:	DOM-19001
Investigational Product:	Revefenacin (YUPELRI™) inhalation solution Formoterol (Perforomist) inhalation solution
Title:	A Phase IV randomized, parallel-group trial to evaluate Feasibility, Safety and Efficacy of Nebulized Long-Acting Bronchodilators (Formoterol and Revefenacin) vs. Short-Acting Bronchodilators (Albuterol and Ipratropium) in Hospitalized Patients with AECOPD
Clinical Phase:	IV
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Status:	Final Protocol (Revised Protocol)

CLINICAL TRIAL PROTOCOL SYNOPSIS

Name of institution: UT Medical Center	
Name of active ingredient: Revefenacin (YUPELRI™) inhalation solution Formoterol (Perforomist®) inhalation solution	
Protocol:	Trial number: DOM-19001
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Principal Investigator :	Rajiv Dhand, MD Department of Medicine University of Tennessee Medical Center Knoxville, TN 37920 USA
Trial sites:	Single center trial
Clinical phase:	IV
Objectives:	The primary aim is to assess the feasibility, safety and efficacy of a combination of nebulized Formoterol and Revefenacin among patients hospitalized for AECOPD compared with standard-of-care therapy with nebulized Albuterol and Ipratropium. Outcomes: Change in Borg Scale Total doses of bronchodilators administered up to 7 days of hospital stay. The need to switch therapy The need for rescue therapy Failure of therapy Side effects.
Methodology:	Randomized, parallel-group
No. of patients:	60
Indication:	Primary diagnosis of AECOPD or acute respiratory failure with a secondary diagnosis of COPD

Main criteria for inclusion:	Patients are ≥ 40 years, of either gender or any race, admitted to the hospital with a primary diagnosis of AECOPD or acute respiratory failure with a secondary diagnosis of COPD. Patients who are hypersensitive to Formoterol or Revefenacin or are unable or unwilling to sign an informed consent or cooperate with study procedures are ineligible. We will also exclude patients who are intubated, have tracheotomy, are receiving mechanical ventilation by mask or artificial airway, have unstable cardiovascular disease (e.g., uncontrolled hypertension, unstable angina, recent MI (within 12 weeks), ventricular arrhythmia, decompensated heart failure), patients, in the opinion of the investigators, who are rapidly decompensating and are immediately in need, or will soon need, ventilator support, those with a current diagnosis of lung cancer requiring treatment, pulmonary diseases other than COPD, lobar pneumonia, acute psychiatric illness, and women who are pregnant or breast feeding.
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Comparators:	Albuterol and Ipratropium every 6 hours (standard)
Test product:	Revefenacin (YUPELRI™) inhalation solution and Formoterol (Perforomist®) inhalation solution
Dose:	Nebulized Revefenacin 175 μg once per day and Formoterol 20 μg twice per day in standard jet nebulizers
Mode of admin:	Oral inhalation via a standard jet nebulizer and wall oxygen
Comparator products: Dose:	Nebulized Albuterol and Ipratropium Every 6 hours Oral inhalation via a standard jet nebulizer and wall oxygen
Duration of treatment:	Up to 7 days
Timing of Dosing:	Nebulizer treatments will be administered by standard jet nebulizers and wall oxygen. Patients will participate in the trial for up to seven days of hospitalization, or hospital discharge, failure of treatment, or death prior to 7 days of hospital stay. Revefenacin will be given between 7am and 9am each morning. Formoterol will be given at that time and between 7pm and 9pm each evening. Short-acting drugs prescribed 4 times per day will be given at the times scheduled by the local bronchodilator protocol.
Criteria for Efficacy	Level of dyspnea assessed by Borg dyspnea scale. The scale will be administered daily immediately prior to AM and PM dosing with bronchodilators Total doses of bronchodilators per day received by each patient Total doses of bronchodilators per hospital stay Number of rescue doses needed per day of hospital stay Number of patients needing to switch / change treatment regimen Failure of treatment (need for mechanical ventilation, or death) Need for supplemental oxygen (lowest level of FiO₂ employed on days 1, 3 and 5 of hospital stay; the respiratory therapist will monitor SpO₂ to determine oxygen requirements)
Criteria for Safety:	Side effects and serious adverse events will be monitored and recorded
Statistical methods:	<u>Safety analysis:</u> Safety endpoints will be summarized in descriptive statistics. <u>Efficacy analysis:</u> Multiple regression models will be used to analyze normally distributed continuous outcomes (level of dyspnea / Borg scale). Poisson or negative binomial regression models will be used to analyze count variables (total doses of bronchodilators, total doses of bronchodilators per hospital stay, number of rescue doses needed per day of hospital stay, number of patients needing to switch/change treatment regimen). Logistic regression models will be used to analyze categorical outcomes (failure of treatment, need for supplemental oxygen) to generate adjusted odds ratios (AOR) with 95% confidence intervals (95% CI).

Table of Contents

ABBREVIATIONS 7

1. INTRODUCTION 8

 1.1 COPD Burden and Treatment 8

 1.2 Lung Hyperinflation 8

 1.3 Treatment (in Context of Hyperinflation) 9

 1.4 Summary and Future Directions 11

2. RATIONALE 11

 2.1 Rationale for Performing the Trial 11

3. Trial Objectives 11

 3.1 Primary Aim 11

 3.2 Outcomes: 12

4. Risk 12

 4.1 New Long-Acting Bronchodilators 12

 4.2 Physical Risks 12

 4.3 Therapeutic Risk 13

 4.4 Psychological Risks: 13

 4.5 Research Risk 13

5. Benefits 13

 5.1 Primary Benefit 13

 5.2 Importance of Knowledge to be gained 14

6. Study Plan 14

 6.1 Study Design 14

 6.2 Study Duration 15

 6.3 Selection of Study Participants 15

 6.3.1 Inclusion Criteria 15

 6.3.2 Exclusion Criteria 15

 6.3.3 Discontinuation of Subjects 15

7. Study Procedures 16

 7.1 Screening Assessments 16

 7.2 Enrollment/Baseline Assessments 16

 7.3 Day 3 Assessments 17

 7.4 Day 7, Discharge, or ET Assessments 17

 7.5 Study Assessment Methods 18

 7.5.1 Concurrent Medication and Medical History Monitoring 18

 7.5.2 Height (cm) & Weight (kg) & BMI 18

7.5.3Vital Signs (BP, HR, O2 level, RR, Temp)	18
7.5.4Borg Dyspnea Scale	18
7.5.5Chest X-Ray.....	19
7.5.6EKG	19
7.5.7Serum Chemistry & Hematology	19
7.5.8Physical Exam	19
7.5.9Randomization.....	19
8. Study SCHEMATIC	20
9. Treatments	20
9.1Treatments to Be Administered.....	21
9.1.1Identity of investigational product and comparator product	21
9.1.2Method of assigning patients to treatment groups	22
9.1.3Selection of doses in the trial	22
9.1.4Drug assignment and administration of doses for each patient	22
9.1.5Blinding	22
9.1.6Packaging, labeling, and re-supply	22
9.1.7Storage conditions	22
9.1.8Drug accountability	22
9.2Concomitant Therapy, Restrictions, and Rescue Treatment.....	23
9.2.1Rescue medication	23
9.3Treatment Compliance.....	23
10. VARIABLES.....	24
10.1Efficacy.....	24
10.1.1Endpoints of efficacy	24
10.2Safety	24
10.2.1Endpoints of safety	24
10.3Adverse Events and Serious Adverse Events	24
10.3.1Adverse Event Definitions	24
10.3.2Unexpected Adverse Event	24
10.3.3Serious Adverse Event	24
10.3.4Adverse Event Assessment and Documentation	25
10.4SAE Reporting.....	26
11. PATIENT RECRUITMENT AND INFORMED CONSENT	26
11.1Informed Consent.....	26
11.2Withdrawal of Consent	27
12. Statistical Methods and Determination of Sample Size	27

12.1 Statistical Design.....	27
12.2 Null and Alternative Hypotheses	27
12.3 Randomization and Statistical Power	27
12.3.1 Randomization	27
12.3.2 Sample Size	28
12.4 Statistical Methods	28
13. Study Management.....	29
13.1 Data Documentation.....	29
13.2 Data Storage	29
13.3 Data Protection.....	29
13.4 Data Confidentiality	30
13.5 Data and Safety Monitoring	30
13.6 Protocol Deviations	30
13.7 Data Quality Assurance.....	31
13.8 RECORDS	31
13.8.1 Source Documents	31
13.8.3 Storage of Records	31
13.9 Completion of Trial	31
14. REFERENCES	32

ABBREVIATIONS

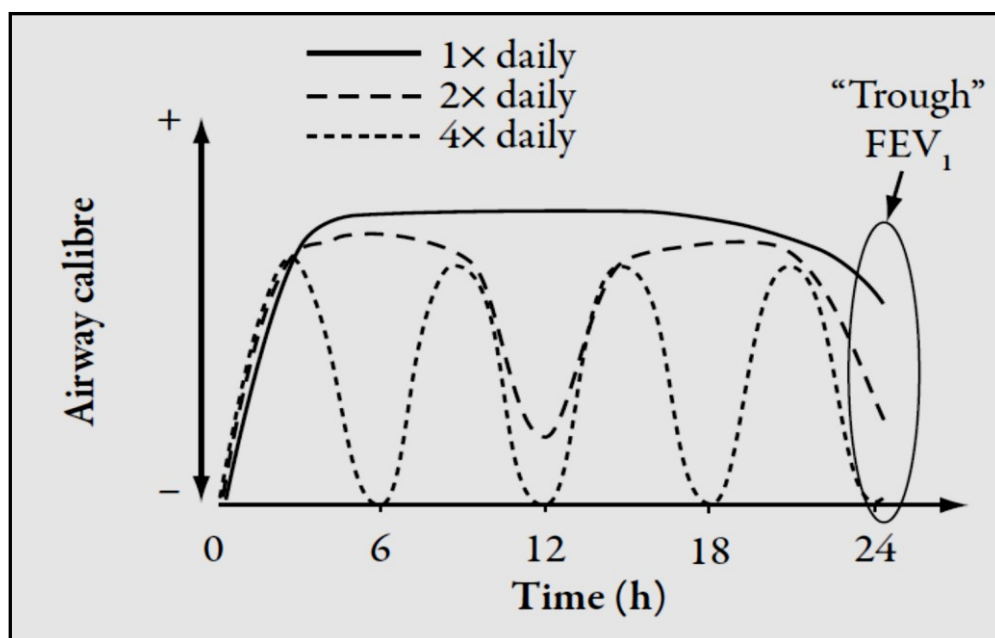
AE	Adverse event
AECOPD	Acute exacerbation of chronic obstructive pulmonary disease
AM	Antemeridian (morning)
ANOVA	Analysis of variance
AOR	Adjusted odds ratio
β ₂	Beta-2
BMI	Body mass index
BP	Blood pressure
CI	Confidence interval
Co-I	Co-Investigator
CMP	Comprehensive metabolic panel
COPD	Chronic obstructive pulmonary disease
CTMF	Clinical trial master file
CTP	Clinical trial protocol
DSMB	Data Safety Monitoring Board
eCRF	Electronic Case Report Form
FDA	Food and Drug Administration
FiO ₂	Fraction of inspired oxygen
FRC	Functional residual capacity
GCP	Good Clinical Practice
GOLD	Global Initiative for Chronic Obstructive Lung Disease
HR	Heart rate
IC	Inspiratory capacity
ICF	Informed Consent Form
ICD	International Classification of Diseases
ICH-GCP	International Conference on Harmonization - Good Clinical Practice
INN	International non-proprietary name
IRB	Institutional Review Board
LABA	Long acting beta-adrenergic
LAMA	Long acting muscarinic receptor antagonist
MCID	Minimum clinically important difference
MI	Myocardial infarction
μg	Microgram
n	Number
O ₂	Oxygen
OR	Odds ratio
PI	Principal Investigator
PM	Postmeridian (evening)
RV	Residual volume
SAE	Serious adverse event
SOC	Standard of Care
SpO ₂	Peripheral capillary oxygen saturation
U.S.	United States
UT	University of Tennessee
UTMC	University of Tennessee Medical Center

1. INTRODUCTION

1.1 COPD Burden and Treatment

Chronic Obstructive Pulmonary Disease (COPD) affects between 6 to 10% of the population over the age of 55 years and is the fourth leading cause of death in the U.S. (Kochanek, 2017). COPD is also associated with significant morbidity. Acute exacerbations, characterized by periods of acutely worsening symptoms that require a change in treatment, punctuate the course of COPD (GOLD, 2019). Severe acute exacerbations of COPD (AECOPD) require treatment in the hospital. The standard-of-care for hospitalized patients with AECOPD is bronchodilators, corticosteroids, antibiotics and supplemental oxygen (GOLD, 2019). The control of dyspnea for most hospitalized patients with AECOPD requires the use of nebulized short-acting bronchodilators, such as Albuterol and Ipratropium every 4-6 hours. Such a regimen is cumbersome and inconvenient for patients, staff, and therapists. Because the frequency of drug administration is predicated on control of symptoms, mainly shortness of breath and chest tightness, the use of short-acting bronchodilators results in frequent breakthrough symptoms as the effect of the drugs wanes within a few hours (**Figure 1**).

Figure 1. Schematic model of the effects of long-acting (once daily or twice daily) versus short-acting (four times daily) bronchodilators on 24-hour airway tone (“pharmacological stenting”).



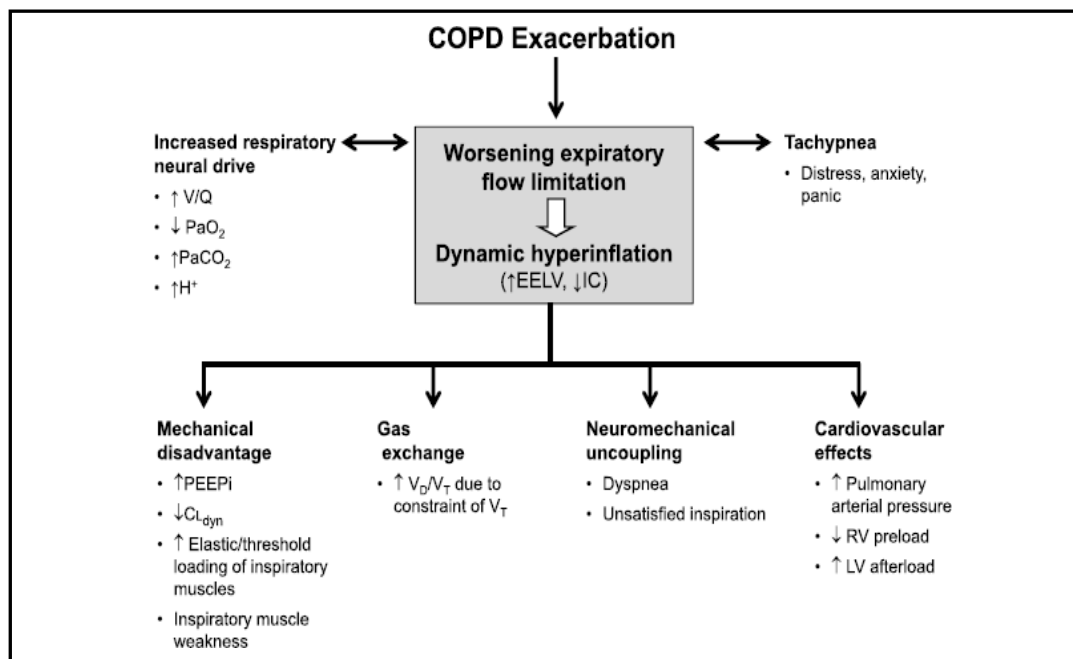
As noted in figure 1, with extended duration of bronchodilation, the net area under the time/airflow curve increases, and persistent bronchorelaxant effects of once daily and twice-daily bronchodilators lead to increased morning forced expiratory volume in 1 second (FEV1) following the last inhalation (“trough” FEV1). Reproduced from Beek KM, Beier J. Adv Ther 2010;27:150-9.

1.2 Lung Hyperinflation

In a significant proportion of people with COPD, reduced lung elastic recoil (due to emphysema) and expiratory flow limitation (due to peripheral airway involvement) leads to lung hyper-inflation during the course of the disease (Gagnon, 2014; O'Donnell, 2015). Increased frequency of breathing (tachypnea), increased respiratory neural drive, and fear or anxiety also contribute to development of dynamic

hyperinflation (**Figure 2**). The effects of lung hyperinflation include increased elastic load, increased inspiratory threshold load, decreased inspiratory muscles pressure generating capacity, impaired gas exchange, impaired cardiopulmonary interaction, mechanical volume restriction, increased functional residual capacity (FRC) and reduced inspiratory capacity (IC) (Gagnon, 2014; O'Donnell, 2015). These pathophysiologic features contribute significantly to the development of dyspnea, exercise intolerance, skeletal muscle limitations, reduced physical activity levels associated with the disease, various morbidities, and mortality (Anzueto, 2010; Gagnon, 2014; O'Donnell, 2015). Lung hyperinflation is commonly increased during severe AECOPD requiring hospitalization (Rossi, 2015; Beeh, 2017) and may, in turn, contribute to a prolonging and/or compounding of the exacerbation. Hence, lung hyperinflation has been recently viewed as a potentially important consideration in AECOPD classification and treatment (van Geffen, 2018; O'Donnell, 2015) (**Figure 2**).

Figure 2: Factors contributing to development of dynamic hyperinflation during AECOPD.



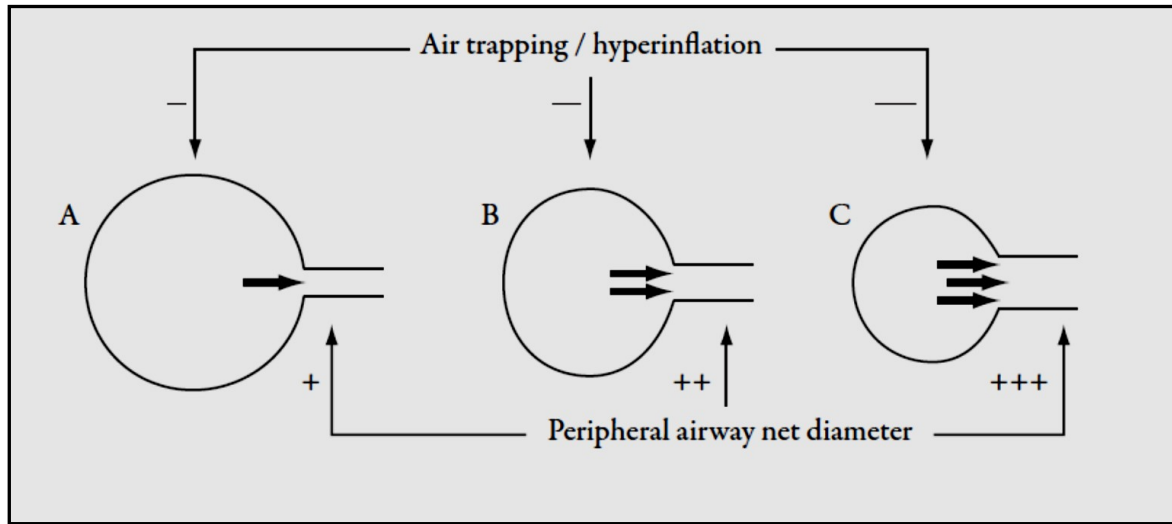
As shown in figure 2, worsening of expiratory flow limitation due to an abrupt increase in airway resistance, increased frequency of breathing, increased respiratory neural drive, and fear or anxiety are major contributors to development of dynamic hyperinflation. As shown in the figure, development of hyperinflation has several negative consequences in such patients. Abbreviations: EELV - end expiratory lung volume; IC - inspiratory capacity; PaO₂ - arterial oxygen tension; PaCO₂ - arterial carbon dioxide tension, PEEPi - intrinsic positive end-expiratory pressure; C_{dyn} - dynamic lung compliance, H⁺ - hydrogen ion concentration; V_D/V_T - physiologic dead space; V/Q - ventilation/perfusion; V_T - tidal volume. Reproduced from O'Donnell DE et al. *COPD Research and Practice* 2015;1:4.

1.3 Treatment (in Context of Hyperinflation)

The major goal of treatment in hospitalized subjects with severe AECOPD is lung deflation by intensive bronchodilator therapy that reduces airway resistance, accelerates time constants for lung emptying, restores neuromechanical coupling and relieves dyspnea. In subjects with COPD, bronchodilators of all classes consistently reduce lung hyperinflation and pulmonary gas trapping, resulting in increases in IC and vital

capacity (VC) (O'Donnell, 2014; Thomas, 2013). Both β_2 -agonists and anti-muscarinic bronchodilators increase IC by ~10-15% in people with COPD (Rossi, 2015; Thomas, 2013), with the largest increase in IC observed in those people with the greatest lung hyperinflation at baseline (Newton, 2002).

Figure 3. Hypothetical model of lung deflation with increased net (area under curve over 24 hours) airway caliber.



As airway patency over time increases with longer duration of bronchodilator action emptying of peripheral airways with trapped air is facilitated, thus reducing hyperinflation and improving breathing mechanics ("pharmacological lung volume reduction"). A=short-acting; B=twice-daily; C=once-daily. Reproduced from Beeh KM, Beier J. *Adv Ther* 2010;27:150-59.

In patients with stable COPD, the combination of beta agonists with anticholinergics produces additive bronchodilation with a good safety profile (Tashkin, 2015). In such patients, long-acting bronchodilators, both anticholinergics and beta-2-adrenergic agonists, provide larger reductions in hyperinflation compared to short-acting bronchodilators (O'Donnell 2017; Mahler, 2015). However, the differential effects of long-acting bronchodilators versus short-acting bronchodilators on hyperinflation have not been determined in patients with AECOPD. Because hyperinflation occurs commonly in patients with AECOPD (Gagnon, 2014; O'Donnell, 2015), and is a major determinant of dyspnea, a greater improvement in dyspnea with long-acting bronchodilators would indicate that they have a more pronounced effect in reducing hyperinflation than short-acting bronchodilators in such patients.

Formoterol is a LABA available as a nebulizer solution (Perforomist, Mylan) that has been employed in patients with AECOPD. Formoterol has a quick onset of action (within 5 minutes), and a 12-hour duration of action.

Long-term use of Formoterol has been shown to have a good safety profile (Hanania, 2019). Formoterol has been employed in combination with a LAMA (tiotropium) given as a dry powder in patients with AECOPD admitted to the hospital (Di Marco, 2006; Drescher 2008). Studies of these drugs have shown that a steadier bronchodilation can be achieved with the use of long-acting bronchodilators, especially a LAMA/LABA combination (Di Marco, 2006). However, there are limited data on the use of long-acting bronchodilators in patients with AECOPD (Di Marco, 2006; Drescher

2008; Tashkin, 2009; Bishwakarma, 2017; Lindenauer, 2014; Amin, 2018; Ganapathy, 2017; Gross, 2008). The advantage of using long acting bronchodilators over short-

acting bronchodilators is that more persistent bronchodilation allows more complete pulmonary emptying during tidal breathing and improves respiratory mechanics, with consequent decrease in dyspnea (**Figure 3**), a reduction of breakthrough symptoms (**Figure 1**), and increase in exercise capacity. However, the effects of long-acting versus short-acting bronchodilators on clinical outcomes have not been compared in patients with AECOPD.

Similarly to Revefenacin, tiotropium has a 24 hour duration of action. As expected, one investigation among patients with mild to moderate AECOPD reported that the combination of Formoterol by metered-dose inhaler (Modulite, Chiesi) and dry powder tiotropium (HandiHaler, Boehringer-Ingelheim) produced greater bronchodilation than either agent alone (Di Marco 2006). Therefore, we anticipate that a combination of nebulized Formoterol and Revefenacin would provide greater and more sustained bronchodilation, and better control of hyperinflation and dyspnea than a combination of nebulized Albuterol and Ipratropium.

1.4 Summary and Future Directions

In recent years, more than 1 million patients were admitted to U.S. hospitals annually suffering from AECOPD, making it one of the leading and most costly causes of adult hospitalizations (Perera, 2012; Gauarascio, 2013). The control of dyspnea currently involves a short-acting bronchodilators regimen that is cumbersome and inconvenient for patients, staff, and therapists and often results in frequent breakthrough symptoms as the effect of the drugs wanes within a few hours. The proposed study is the first to address the feasibility, safety and efficacy of long-acting bronchodilator once daily Revefenacin with twice daily Formoterol versus standard treatment with short-acting bronchodilators in hospitalized patients with AECOPD. This study is also the first to evaluate whether long-acting bronchodilators improve dyspnea in patients with AECOPD to a greater extent than short-acting bronchodilators. As such, the results of this study will inform future studies on the effects of long-acting bronchodilators on hospital length of stay, failure of treatment, and mortality in hospitalized patients with AECOPD. In future, we anticipate that nebulized Revefenacin and Formoterol could be the standard-of-care regimen for hospitalized patients with AECOPD.

2. RATIONALE

2.1 Rationale for Performing the Trial

To control dyspnea symptoms, most patients in the hospital receive nebulized Albuterol and Ipratropium every 4-6 hours and tend to suffer recurring symptoms towards the end of each treatment cycle ("peaks and troughs"). A combination of a LAMA/LABA may ultimately prove more effective in treating dyspnea symptoms with fewer doses and reduced costs. To date, however, Revefenacin has not been studied in patients hospitalized for AECOPD. Therefore, it is unclear whether once daily Revefenacin via jet nebulizer (LAMA) in combination with a LABA (Formoterol twice daily) can feasibly and safely replace the standard treatment with short-acting bronchodilators in hospitalized patients with AECOPD. To the best of our knowledge, the effect of a nebulized Formoterol and Revefenacin combination on clinical outcomes has not been previously investigated in patients with AECOPD.

3. TRIAL OBJECTIVES

3.1 Primary Aim

The **primary aim** is to assess the feasibility, safety and efficacy of a combination of nebulized Formoterol and Revefenacin among patients hospitalized for AECOPD compared with standard-of-care therapy with nebulized Albuterol and Ipratropium.

3.2 Outcomes:

- Borg Dyspnea Scale
- Total doses of bronchodilators administered up to 7 days of hospital stay
- The need to switch therapy
- The need for rescue therapy
- Failure of therapy
- Side effects

We hypothesize that in patients hospitalized for AECOPD, treatment with nebulized Revefenacin and Formoterol will improve symptoms, enhance convenience (through treatment dose reduction) and safety. The long-acting bronchodilator regimen will provide symptom control with fewer total doses and patients will experience less breakthrough dyspnea from “peaks and troughs” of bronchodilator effect compared with standard treatment with short-acting bronchodilators, namely, nebulized Albuterol and Ipratropium. To the best of our knowledge, this will be first investigation to prospectively compare a combination of long-acting nebulized LAMA/LABA bronchodilators with a standard-of-care combination of short-acting nebulized SAMA/SABA bronchodilators in patients with AECOPD.

4. RISK

4.1 New Long-Acting Bronchodilators

Long-acting bronchodilators, beta-agonists (LABAs) and anticholinergics (LAMAs), are approved for management of stable COPD. A few previous studies have examined the use of LABAs and LAMAs in hospitalized patients with AECOPD (Di Marco, 2006; Drescher, 2008). However, given such issues as the lack of a short-acting drug comparison group (Di Marco, 2006), limitations of sample size, scope, and patients with severe AECOPD (Di Marco, 2006), and the lack of a randomized study design (Drescher, 2008), it is uncertain whether the results of these studies are generalizable or robust. Another limitation to using long-acting bronchodilators is that, until recently, there was no nebulized formulation of a LAMA for use in acutely ill patients. Glycopyrrolate was the first LAMA that was approved in a nebulizer solution. However, glycopyrrolate requires a specialized nebulizer for delivery (Lonhala Magnair, Sunovion). New to the market, Revefenacin (YUPELRI™) inhalation solution, a LAMA developed by Theravance Biopharma and Mylan, is the first and currently the only once-daily, nebulized bronchodilator to be approved for the treatment of COPD. Revefenacin is a potent LAMA that binds competitively and reversibly to the M₃ receptors in the airway smooth muscle, thereby inhibiting bronchoconstriction and increasing bronchodilation (Heo, 2019).

Administered via a standard jet nebulizer, Revefenacin has been generally well tolerated, with minimal reports of systemic anti-cholinergic effects (Pudi, 2017). In November 2018, based on results of two phase III trials (Ferguson et al 2019), the US FDA granted market approval to Revefenacin for the maintenance treatment of patients with COPD. To the best of our knowledge, Revefenacin has not been formally investigated for treatment of hospitalized patients with AECOPD.

4.2 Physical Risks

Although the medications being used in this protocol have been FDA approved and well tested for efficacy and safety, there may be potential risks associated with participation. Any medication can have temporary and permanent side effects and can cause unforeseen adverse reactions, intolerance, or worsening of co-morbidities (including, glaucoma, urinary retention, and renal and hepatic impairment), which could lead to prolonged hospitalization, life-threatening illness, and or death. Any subject with known medical conditions, or on a concurrent medication in which the study medications are not recommended, will be excluded from participation. The medication forms and doses in this study have been used extensively in treating COPD

patients. They are “real world” treatments that are currently in the standard of care. The drugs used in this study are currently in common use and will be administered in dosages currently approved for those drugs. Patients will be carefully screened for contraindications to participation prior to study enrollment. We will monitor for potential side effects in randomized patients.

Serious allergic reactions to study medications is a potential risk. Symptoms of allergic reactions include rash, difficulty breathing, coughing, wheezing, sudden drop in blood pressure, swelling of the mouth, throat or eyes, seizures, flushing, a fast pulse, and sweating. A severe allergic reaction could be life-threatening, and may result in death, although highly unlikely.

Potential side effects for study drug interventions include the following:

Revefenacin: Potential side effects include paradoxical bronchospasm, cough, nasopharyngitis, upper respiratory infection, headache and back pain.

Formoterol: Potential side effects include headache, tremor, nervousness, dry mouth, muscle cramps, nausea, vomiting, diarrhea, dizziness, tiredness, and trouble sleeping.

4.3 Therapeutic Risk

There is the potential risk of a therapeutic failure for study participants. The study results may not support the primary hypothesis that, in patients hospitalized for AECOPD, treatment with nebulized Revefenacin and Formoterol will improve symptoms, reduce overall treatment dose, and improve safety. It is possible that the experimental treatment regimen (nebulized Revefenacin 175 μ g once per day and Formoterol 20 μ g twice per day) will prove to be less effective than the standard (Albuterol and Ipratropium every 6 hours). In comparison, patients in the experimental group may experience greater dyspnea symptoms, greater need for rescue medicines and/or supplemental oxygen, and greater failure of treatment (mechanical ventilation, or death).

4.4 Psychological Risks:

A potential psychological risk could occur if patients feel a sense of coercion to participate in the trial. The likelihood is small, because patients will be assured in the informed consent document and face-to-face discussion that participation is purely voluntary.

4.5 Research Risk

No identifiable patient information will be linked to patient assessments during the study. For this specific project, all information related to patients will be identified only by patient initials and study serial number. The greatest research risk, although rare, is the loss of confidentiality caused by unauthorized release or misuse of information from research records.

5. BENEFITS

5.1 Primary Benefit

Although there may be immediate clinical benefits for some patients in this trial who are assigned to receiving newer long-acting drugs, the anticipated primary benefit is the future potential to reduce symptoms, medical complications, and a significant reduction in personal, health care and societal costs associated with hospitalizations for AECOPD.

Information obtained from this research may help patients in future achieve better health outcomes and provide clinicians with pertinent information about treating AECOPD during hospitalizations. The treatment may be more effective than the treatments that are currently available.

5.2 Importance of Knowledge to be gained

AECOPD results in approximately 800,000 hospitalizations in the U.S. each year, which has profound clinical implications for patients, poses significant burdens on the healthcare system, and has large economic consequences for society (Krishnan and Prieto-Centurian, 2017). Hospitalization for AECOPD is one of the leading and most costly causes of adult hospitalizations (Perera, 2012; Gauarascio, 2013). The control of dyspnea currently involves a short-acting bronchodilators regimen that is cumbersome and inconvenient for patients, staff, and therapists and often results in frequent breakthrough symptoms as the effect of the drugs wanes within a few hours. The proposed study is the first to address the feasibility, safety and efficacy of long- acting bronchodilator once daily Revefenacin with twice daily Formoterol versus standard treatment with short-acting bronchodilators in hospitalized patients with AECOPD. This study is also the first to evaluate whether long-acting bronchodilators improve dyspnea in patients with AECOPD to a greater extent than short- acting bronchodilators. As such, the results of this study will inform future studies on the effects of long- acting bronchodilators on hospital length of stay, failure of treatment, and mortality in hospitalized patients with AECOPD. In future, we anticipate that nebulized Revefenacin and Formoterol could be the standard-of- care regimen for hospitalized patients with AECOPD.

6. STUDY PLAN

6.1 Study Design

A prospective, parallel group, randomized clinical trial in 60 patients hospitalized with the primary diagnosis of AECOPD or acute respiratory failure with a secondary diagnosis of COPD (ICD-10 codes J44.1 and J96 - J96.2 with J44.9).

The plan is to:

- Compare the feasibility, safety and efficacy of standard bronchodilator protocol with nebulized Albuterol and Ipratropium every 6 hours (n=30) versus nebulized Revefenacin 175 μ g once per day and Formoterol 20 μ g twice per day (n=30) for up to 7 days of treatment. Study medication will be administered by standard jet nebulizers in both groups.
- Assess level of dyspnea via Borg dyspnea scale twice a day during hospitalization post dosing with bronchodilators
- Record the total doses of bronchodilators per day received by each patient
- Record the number of rescue doses needed per day of hospital stay
- Record the number of patients needing to switch / change treatment regimen
- Record the need for supplemental oxygen (lowest level of FiO₂ employed on days 1, 3 and 7 of hospital stay)
- Record all adverse events
- Monitor for safety
 - Physical Exam (Day 1, 3, 7, or ET)
 - Concurrent Medication Monitoring (Day 1, 3, 7, or ET)
 - Serum Chemistry (Day 1, 3, 7, or ET). Standard of care (SOC) laboratory results are acceptable
 - Hematology (Day 1, 3, 7, or ET). Standard of care (SOC) laboratory results are acceptable
 - Chest X-Ray (Day 1). Admission x-ray completed during standard of care is acceptable

6.2 Study Duration

We plan to enroll ~ 5 patients per month for 12 months. The total study duration will be approximately 15 months post IRB approval and study initiation.

6.3 Selection of Study Participants

Patients admitted to UT Medical Center who meet the predefined inclusion and exclusion criteria will be enrolled within 24-36 hours of admission. The nature and purpose of the study will be explained to the patient by one of the investigators and the patient will be given a copy of the informed consent to review. The investigator or study coordinator will answer any questions which the patient may have prior to their signing the consent. The signed informed consent will be kept in the patient's research chart and a copy will be given to the patient. No study related interventions will be performed until the patient signs the informed consent.

6.3.1 Inclusion Criteria

- 1 Male or Female
- 2 Any Race
- 3 ≥ 40 years of age
- 4 Admitted to the hospital with a primary diagnosis of AECOPD or acute respiratory failure with a secondary diagnosis of COPD
- 5 Able to understand and comply with study procedures
- 6 Willingness to sign and date an Informed Consent Form

6.3.2 Exclusion Criteria

- 1 Patients unable or unwilling to sign an informed consent or cooperate with study procedures
- 2 Patients who are hypersensitive to Formoterol or Roflumetolol
- 3 Patients who are intubated, have tracheotomy, are receiving mechanical ventilation by mask or artificial airway
- 4 Patients, in the opinion of the investigators, who are rapidly decompensating and are immediately in need, or will soon need, ventilator support
- 5 Patients who, per the investigator, have unstable cardiovascular disease (e.g., uncontrolled hypertension, unstable angina, recent MI (within 12 weeks), ventricular arrhythmia, or decompensated heart failure)
- 6 Patients with a current diagnosis of lung cancer requiring treatment
- 7 Patients that test positive for COVID-19
- 8 Pulmonary diseases other than COPD, or lobar pneumonia
- 9 Patients with acute psychiatric illness deemed significant by the investigator
- 10 Patients with a history of glaucoma deemed significant by the investigator
- 11 History of urinary retention deemed significant by the investigator
- 12 Women who are pregnant or breast feeding

6.3.3 Discontinuation of Subjects

An individual patient is to be withdrawn from the trial if any of the following criteria apply:

- The patient withdraws consent, without the need to justify the decision
- The patient is no longer able to participate for medical reasons (e.g., surgery, AEs, or other diseases)
- Decision by the PI to discontinue a specific patient for his/her safety (e.g., in case of SAEs)
- The sponsor (Mylan Pharmaceuticals) reserves the right to discontinue the trial at any time for reasons

such as failure to meet expected enrolment goals, or the emergence of any efficacy/safety information that could significantly affect continuation of the trial

Data of patients who discontinue or withdraw prior to randomization will be entered in the trial database and will be listed. Data of patients who discontinue or withdraw after randomization will be documented and the reason for withdrawal will be recorded in the electronic case report form (eCRF). The data will be included in the trial database and will be reported.

7. STUDY PROCEDURES

7.1 Screening Assessments

Screening assessments should be completed within 24-36 hours post hospital admission. Assessments will be initiated after the Informed Consent Form (ICF) Process. The PI and study designee will present the study information to the patient. They will explain the purpose, risk, and benefits to the subject and then present them with an IRB approved ICF. The potential participant will be given ample time to read the ICF and all questions and concerns from the subject will be addressed by the PI and study team member. No procedures will be initiated prior to the subject signing and dating the ICF. After the subject signs the ICF, a copy will be given to them for their records. Participants will be informed that they can decline participation in the study without any effect on their health care. They can also withdraw their consent, including the consent to do various tests, at any time.

- Informed Consent
- Medical History Review for Exclusion Criteria
- Concurrent Medication Review
- Borg Dyspnea Scale
- Review of inpatient laboratory results (CMP or BMP, COVID test, Hematology)
- Review of Inclusion / Exclusion Criteria
- Confirmation of Subject eligibility by PI or study designee representative on eligibility form.

7.2 Enrollment/Baseline Assessments

Enrollment/Baseline assessments can be completed on the same day as the screening visit as long as all enrollment criteria have been confirmed. Baseline assessments should be completed within 24-36 hours post hospital admission. Assessments will be performed on the hospital floor at the patient's bedside, other than the Chest X-Ray, which will be performed in the radiology department. All procedures must be completed and reviewed prior to randomization. Laboratory results can be reviewed post visit completion as long as previous chemistry and hematology samples from current admission are available in the medical chart.

- Concurrent Medication Monitoring
- Medical History Review
- Height (cm) & Weight (kg)
- BMI
- Vital Signs (BP, HR, O2 level, RR, Temp)
- Borg Dyspnea Scale (completed twice every day during subject participation)
- Chest X-Ray
- EKG

- Serum Chemistry or BMP
- Hematology
- Physical Exam
- Confirm Inclusion & Exclusion Criteria
- Randomization
- Study drug Assignment
- Study drug Administration

Any SOC chest x-ray, hematology, chemistry, EKG, and set of vital signs collected on scheduled study visit days are acceptable to record. Measurements may be repeated if needed.

7.3 Day 3 Assessments

Day 3 assessments will be completed on the third day of study medication use. The study coordinator will review the subject's concurrent medication and medical history. They will question the subjects for any possible side-effects or adverse events. If side-effects or adverse events are reported, the PI will assess for causality, severity, intervention, and outcomes. The following procedures will be completed.

- Medical History Review
- Concurrent Medication Monitoring
- Adverse Event Monitoring
- Height (cm) & Weight (kg)
- BMI
- Vital Signs (BP, HR, O2 level, RR, Temp)
- ECG
- Borg Dyspnea Scale (completed twice every day during subject participation)
- Serum Chemistry
- Hematology
- Physical Exam (including response to therapy)
- Study drug log completion

Any SOC chest x-ray, hematology, chemistry, EKG, and set of vital signs collected on scheduled study visit days (or within 24 hours) are acceptable to record. Measurements may be repeated if needed.

7.4 Day 7, Discharge, or ET Assessments

Day 7, discharge, or ET assessments will be completed on the 7th day of study medication use or on the day of discharge, if it occurs before the 7th day of treatment. The study coordinator will review the subject's concurrent medication and medical history. They will question the subjects for any possible side-effects or adverse events. If side-effects or adverse events are reported, the PI will assess for causality, severity, intervention, and outcomes. If the subject is an ET, the study team designee will record the reason for withdrawal. The following procedures will be completed:

- Medical History Review

- Concurrent Medication Monitoring

- Adverse Event Monitoring
- Height (cm) & Weight (kg)
- BMI
- Vital Signs (BP, HR, O2 level, RR, Temp)
- EKG
- Borg Dyspnea Scale (completed twice every day during subject participation)
- Serum Chemistry
- Hematology
- Chest X-Ray
- Physical Exam (Including response to therapy)
- Study drug log completion

Any SOC chest x-ray, hematology, chemistry, ECG, and set of vital signs collected on scheduled study visit days (or within 24 hours) are acceptable to record. Measurements may be repeated if needed.

7.5 Study Assessment Methods

7.5.1 Concurrent Medication and Medical History Monitoring

The PI, study coordinator, or Co-I will review the subject's medical history and concurrent medications at screening. The start and stop dates will be recorded for each chronic or recurrent medical diagnosis and surgical history, along with their admitting diagnoses will be recorded on the medical history log in the subject's source document. The subject's current medications, including home medication taken in the last two weeks prior to their hospitalization, and any medications taken during hospitalization will be recorded on the medication log in the subject's source document. The start date, indication, dosage, route, and duration of treatment will be recorded. If any date is unknown, *UN* or *UNK* will be used.

7.5.2 Height (cm) & Weight (kg) & BMI

Verbal verification of height from the subject is acceptable for this protocol. Weight should be measured from a free standing scale on the hospital floor if one is available or from a portable scale. If the subject is unable to safely maneuver to a scale, or one is not available, the subject's hospital bed may be used to obtain a weight.

$$\text{BMI} = (\text{Weight (lbs)} \times 703 / (\text{Height (in)}^2))$$

7.5.3 Vital Signs (BP, HR, O2 level, RR, Temp)

Vital signs including BP, HR, O2 level, RR, and temperature should be taken at all visits prior to any other procedures. On the day of randomization, vital signs should be recorded, and documented in the subjects source document, prior to dosing the subject with study drug. For consecutive visits after randomization, vital signs should be recorded prior to dosing when possible, but this may be difficult due to required dosing times.

7.5.4 Borg Dyspnea Scale

The Borg Scale was originally developed to measure perceived exertion, and subsequently was used to measure breathlessness; now the Modified Borg Scale is the format most commonly used (Bausewein 2007). The Modified Borg was designed to measure the degree of breathlessness on a 10-point numerical scale from 1 (very slight) to 10 (maximal). The scale is considered to be a valid

and reliable assessment tool for dyspnea in COPD patients (Kendrick, 2000).

The Borg Dyspnea Scale will be administered daily by the respiratory therapist twice a day for subjects in both treatment groups prior to study drug dosing. The completed questionnaire will be filed in the subject's source document.

7.5.5Chest X-Ray

A chest x-ray to eliminate any other type of serious lung disease must be completed prior to randomization. A chest x-ray collected through standard of care during the subjects current hospital admission is acceptable. If there is not an available chest x-ray, this must be completed by the study team prior to enrollment.

7.5.6EKG

An EKG to eliminate any type of significant prolonged QTC must be completed prior to randomization. An EKG collected through standard of care during the subject's current hospital admission is acceptable. If there is not an available EKG, this must be completed by the study team prior to enrollment. EKG's obtained via SOC within 24 hours of the scheduled day 3, 7, or ET visit is acceptable to use for study purposes.

7.5.7Serum Chemistry/BMP & Hematology

A Chemistry and Hematology panel to confirm inclusion and exclusion criteria (to rule out significant kidney and hepatic impairments) must be completed prior to randomization. A Chemistry and Hematology panel collected through standard of care during the subject's current hospital admission is acceptable. If there is not an available Chemistry or BMP and Hematology panel, this must be completed by the study team prior to enrollment. A Chemistry and Hematology panel collected via SOC within 24 hours of the scheduled day 3, 7, or ET visit is acceptable to use for study purposes.

7.5.8Physical Exam

The physical exam will be completed by the investigator prior to enrollment at day 1. The PI, or sub investigator will continue to monitor the subject at each sequential visit for any significant changes from baseline.

7.5.9Randomization

Randomization will be according to a pre-determined pseudo-random-number computer generated schedule developed by the biostatistician. Only the study investigators will know the randomization schedule.

7.5.9.1Study drug Assignment

After enrolment, each subject will be assigned a study number. The subject will receive the bronchodilator (short-acting / long-acting) drug regimen previously allocated to that study number. The pharmacist will confirm the drug assignment and dispense the drugs corresponding to the allocated regimen.

7.5.9.2Study drug Administration

Nebulizer treatments will be administered by jet nebulizers and wall oxygen. Patients will participate in the trial for up to seven days of hospitalization, or hospital discharge, failure of treatment, or death prior to 7 days of hospital stay. Revefenacin will be given between 7am and 9am each morning. Formoterol will be given at that time and between 7pm and 9pm each evening. Short-acting drugs prescribed 4 times per day will be given at the times scheduled by the local bronchodilator protocol. All study participants will continue taking other medication as prescribed, such as enteral or parenteral corticosteroids, beta-blockers, inhaled corticosteroids, diuretics, oxygen, parenteral antibiotics, etc., according to the recommendation of their treating physicians. Other long-acting bronchodilators, except Formoterol and Revefenacin, will not be permitted. Nebulized Albuterol and

Ipratropium will be provided for breakthrough symptoms in both groups.

8. STUDY SCHEMATIC

Required Assessments	Screening	Baseline Day 1	Day 3	Day 7	ET
Informed Consent	x				
Verify Medical History	x	x	x	x	x
Verify Concurrent Medications	x	x	x	x	x
Eligibility Questionnaire	x				
Height	x	x	x	x	x
Weight	x	x	x	x	x
BMI	x	x	x	x	x
Vital Signs (BP, HR, O2, RR, Temp)*♦	x	x	x	x	x
Borg Dyspnea Scale † (Daily and at each visit)	x	x	x	x	x
Chest x-ray♦	x				
ECG♦	x	x	x	x	x
Serum Chemistry♦	x	x	x	x	x
Physical Exam	x	x	x	x	x
Randomization and Dispensing of Treatment		x			
Drug Accountability Log		x	x	x	x
Medication Administration°					
Adverse Event Assessment		x	x	x	x
*Taken prior to drug administration if possible. ♦ Any SOC chest x-ray, chemistry, ECG, and vital signs collected on scheduled study visit days (or within 24 hours) are acceptable to record. Repeated measures may be collected if needed. † To be completed twice per day prior to the AM and PM doses of study drug everyday during the subjects participation in each group. °Study medication is administered everyday per the protocol from day 1– day 7, or ET.					

9. Treatments

The treatment has been selected to evaluate the feasibility, safety and efficacy of Nebulized Long-Acting Bronchodilators (Formoterol and Revefenacin) vs. Short-Acting Bronchodilators (Albuterol and Ipratropium) in Hospitalized Patients with AECOPD. However, this study is not designed to detect any difference of the two treatment regimens in terms of overall clinical outcomes such as mortality, duration of hospital stay, or incidence of any specific AE.

Although relatively new to the market, Revefenacin (YUPELRI™) inhalation solution was approved by the US FDA for the maintenance treatment of patients with COPD. Administered via a standard jet nebulizer, Revefenacin has been generally well tolerated, with minimal reports of systemic anti-cholinergic effects (Pudi, 2017). Formoterol is a LABA available as a nebulizer solution (Perforomist, Mylan) that has been employed in patients with AECOPD with a good safety profile (Hanania, 2019).

A combination of inhaled Albuterol and Ipratropium is a widely used, standard treatment for patients hospitalized with AECOPD (GOLD, 2019). Therefore, we will compare the feasibility, safety and efficacy of this standard bronchodilator protocol (nebulized Albuterol and Ipratropium every 6 hours) versus nebulized Revefenacin 175 μg once per day and Formoterol 20 μg twice per day.

9.1 Treatments to Be Administered

Patients will be randomized 1:1 to a standard bronchodilator protocol with nebulized Revefenacin 175 μg once per day and Formoterol 20 μg twice per day (n=30) versus Albuterol and Ipratropium every 6 hours (n=30) nebulized over the 7-day treatment period. The treatment assignment will not be blinded.

Revefenacin will be given between 7am and 9am each morning. Formoterol will be given at that time and between 7pm and 9pm each evening. Short-acting drugs prescribed 4 times per day will be given at the times scheduled by the local bronchodilator protocol.

Group 1: Revefenacin (YUPELRI) & Formoterol (Perforomist), or

Group 2: Ipratropium Bromide (Atrovent) & Albuterol (Ventolin) as Standard of Care.

9.1.1 Identity of investigational product and comparator product

Investigational product - 175 μg Revefenacin (INN):	Revefenacin
Pharmaceutical form:	inhalation solution
Unit strength:	175 μg
Device:	Jet nebulizer
Posology:	Once daily (in the morning)
Route of administration:	oral inhalation
Investigational product - 20 μg Formoterol (INN):	Formoterol fumarate
Pharmaceutical form:	inhalation solution
Unit strength:	20 μg
Device:	Jet nebulizer
Posology:	Twice daily (morning an evening)
Route of administration:	oral inhalation

Investigational product - 2.5 mg Albuterol (INN):	Albuterol sulfate
Pharmaceutical form:	inhalation solution
Unit strength:	2.5 mg
Device:	Jet nebulizer
Posology:	4 times daily (per standard protocol)
Route of administration:	oral inhalation
Investigational product - 500 μg Ipratropium (INN):	Ipratropium bromide
Pharmaceutical form:	inhalation solution
Unit strength:	500 μg
Device:	Jet nebulizer
Posology:	4 times daily (per standard protocol)
Route of administration:	oral inhalation

IRB NUMBER: 4586

IRB APPROVAL DATE: 09/14/2020

9.1.2 Method of assigning patients to treatment groups

When a patient is qualified for entry into the randomized treatment period, treatment assignment will be made by means of a randomization table prepared by a third-party biostatistician.

9.1.3 Selection of doses in the trial

9.1.3.1 Revefenacin

Two completed clinical trials (Ferguson et al, 2019) provide evidence that Revefenacin 175 µg is effective, and superior to 88 µg. Once daily administration of 175 µg of Revefenacin for 12 weeks demonstrated clinically significant improvements in FEV₁ and trough FEV₁. Revefenacin in those trials was generally well tolerated with no major safety concerns.

9.1.3.2 Formoterol

Formoterol is a LABA available as a nebulizer solution (Perforomist, Mylan) that has been employed in patients with AECOPD. Long-term use of Formoterol has been shown to have a good safety profile (Hanania, 2019).

Formoterol (20 µg twice daily) has been employed in combination with a LAMA (tiotropium) given as a dry powder in patients with AECOPD admitted to the hospital (Di Marco, 2006; Drescher 2008).

9.1.4 Drug assignment and administration of doses for each patient

Dispensing of study medication

Patients will be randomized at screening to one of the two treatment groups. Study medication will be dispensed to the patient by the investigator/pharmacist after randomization. The amount of study medication dispensed will be recorded on the drug accountability forms.

9.1.5 Blinding

Treatment assignment will not be blinded in this trial.

9.1.6 Packaging, labeling, and re-supply

All medications will be supplied in pre-packaged and labeled nebules containing one dose of each medication. The sponsors will provide enough medication to treat each study participant for 7 days.

9.1.7 Storage conditions

All clinical trial supplies will be stored in a locked, secure cabinet and will be kept in their original packaging under the recommended storage conditions and may only be dispensed to trial subjects according to protocol. Trial supplies should not be frozen.

A temperature log must be maintained at the site. If the storage conditions are found to be outside the specified range, the study team will immediately contact the PI.

9.1.8 Drug accountability

Drug supplies, which will be provided by the sponsor, will be kept in a secure, limited access storage area under the storage conditions defined by the sponsor. Where necessary, a temperature log will be maintained to make certain that the drug supplies are stored at the correct temperature. The investigational drug pharmacist will receive the investigational drugs delivered by the sponsor when the following requirements are fulfilled:

- Approval of the study protocol by the institutional review board (IRB),
- Availability of a signed and dated clinical trial contract between the sponsor and the PI,
- Approval/notification of the regulatory authority, e.g. competent authority,
- Availability of the curriculum vitae of the principal investigator,
- Availability of a signed and dated CTP.

The investigational drug pharmacist and coordinator will maintain records of the product's delivery to the trial site, the inventory at the site, the use by each patient, and the return to the sponsor or alternative disposition of unused products.

These records will include dates, quantities, batch/serial numbers, expiry ('use by') dates, and the unique code numbers assigned to the investigational products and trial patients. The investigational drug storage manager will maintain records that document adequately that the patients were provided the doses specified by the CTP and reconcile all investigational products received from the sponsor.

The investigational drug pharmacist should return the unused and collected investigational drugs (including empty boxes) to the sponsor after the trial.

Upon completion of the trial, the investigational drug pharmacist submits to the sponsor a copy of the investigational drug reconciliation log.

Rescue medication in this trial (Albuterol and Ipratropium) is considered a non-investigational medicinal product. Source data documentation and full drug accountability in regard to dispensed and returned medication to investigational site and to patients are required.

9.2 Concomitant Therapy, Restrictions, and Rescue Treatment

9.2.1 Rescue medication

Administration of rescue medication is allowed at any point during the trial. Nebulized Albuterol and Ipratropium will be provided for breakthrough symptoms in both groups. The frequency and timing of such rescue treatments will be recorded.

9.2.1.2 Emergency procedures

There are no special emergency procedures to be followed.

9.2.1.3 Additional treatments

All study participants will continue taking other medication as prescribed, such as enteral or parenteral corticosteroids, beta-blockers, inhaled corticosteroids, diuretics, oxygen, parenteral antibiotics, etc., according to the recommendation of their treating physicians. Other long-acting bronchodilators, except Formoterol and Revefenacin, will not be permitted. The frequency and timing of use of these treatments will be recorded.

9.3 Treatment Compliance

Compliance will be guaranteed by administration of the trial drug under supervision of the investigating physician or designee.

10. VARIABLES

10.1 Efficacy

10.1.1 Endpoints of efficacy

1. Level of dyspnea assessed by Borg dyspnea scale. The scale will be administered daily immediately prior to AM and PM dosing with bronchodilators
2. Total doses of bronchodilators per day received by each patient
3. Total doses of bronchodilators per hospital stay
4. Number of rescue doses needed per day of hospital stay
5. Number of patients needing to switch / change treatment regimen
6. Failure of treatment (need for mechanical ventilation, or death)
7. Need for supplemental oxygen (lowest level of FiO₂ employed on days 1, 3 and 5 of hospital stay; the respiratory therapist will monitor SpO₂ to determine oxygen requirements)

10.2 Safety

10.2.1 Endpoints of safety

1. Number of related AE(s)
2. Number of related SAE(S)
2. Side effects reported by subjects or observed by study team
3. Stability of study participants' vital signs and laboratory evaluations

10.3 Adverse Events and Serious Adverse Events

10.3.1 Adverse Event Definitions

An adverse event (AE) is any untoward medical occurrence that may present itself during the course of a research study. An AE can be any unfavorable and unintended sign, symptom, or disease temporally associated with the patient's participation in the research study, regardless of the suspected cause.

10.3.2 Unexpected Adverse Event

An unanticipated or unexpected adverse event is a medical occurrence whose nature, severity or frequency is not consistent with existing information regarding the risk profile of the study procedure.

10.3.3 Serious Adverse Event

A serious adverse event (SAE) is a medical condition that results in one of the following:

- Death
- Is life threatening
- Requires inpatient hospitalization or prolongs an existing hospitalization
- Creates persistent or significant disability or incapacity
- Results in a congenital anomaly or birth defect

An important medical event that may not result in death, be life threatening, or require hospitalization may be considered a SAE when, based upon appropriate medical judgment, it may require medical or surgical intervention to prevent one of the outcomes noted above.

Life threatening: an SAE considered life threatening refers to an adverse event in which the patient was at risk of death at the time of the event. It does not refer to an AE which hypothetically might have caused death if it were more severe.

10.3.4 Adverse Event Assessment and Documentation

AEs that are considered possibly, probably or definitely related to the study procedure will be recorded in the CRFs. AEs will be assessed starting with onset, and evaluation will continue until resolution is noted, or until the investigator determines that the patient's condition is stable.

All AEs will be characterized by the following:

- AE name
- Start and Stop dates
- Relationship to study procedure
- Severity
- Action taken
- Outcome

10.3.4.1 Relationship

The investigators will assess the AEs and using their clinical judgment will assign an attribution to the AE using the following categories:

- **Unrelated** - The AE *is clearly NOT related* to the study procedure
- **Unlikely** - The AE *is doubtfully related* to the intervention
- **Possibly** - The AE *may be related* to the study procedure
- **Probably** - The AE *is likely related* to the study procedure
- **Definitely** - The AE *is clearly related* to the study procedure

10.3.4.2 Severity

The severity of the AEs should be graded by the investigator as follows:

- **Mild** - Transient discomfort; no prescribed medical intervention/therapy required and does not interfere with daily activities.
- **Moderate** - Low level of discomfort or concern with mild to moderate limitation in daily activities; some assistance may be needed; medical intervention/therapy required.
- **Severe** - Discomfort and limitation in daily activities, assistance required; medical intervention/therapy required.

10.3.4.3 Action Taken

The action taken in response to the AE should be reported using the following categories:

- None
- Procedure or physical therapy
- Withdrawn from study due to AE
- Hospitalization

- Prescription drug therapy
- Non-prescription drug therapy
- Other (specify)

10.3.4. Outcome

The clinical outcome of an AE should be characterized as follows:

- Resolved without sequelae
- Resolved with sequelae (specify)
- Ongoing (i.e. continuing at time of study discontinuation)
- Death
- Unknown/lost to follow-up
- Other

10.4 SAE Reporting

All SAEs will be documented in the CRFs. SAEs will be reported to the local IRB per the following guidelines:

Adverse event reports will only be submitted to the local IRB if they are determined by the principal investigator to be: unanticipated, serious, and possibly, probably or definitely related to a research study procedure.

SAEs meeting these criteria (except for deaths) must be reported to the IRB *within 5 working days* of the study team's notification of occurrence. Deaths that are unanticipated and are possibly, probably or definitely related to a research study procedure must be reported to the IRB *within 24 hours* of notification of occurrence.

Any relevant follow-up information regarding the SAE should be submitted to the IRB as soon as it becomes available and/or upon request.

SAE reports to the IRB must include the following: subject identifier, adverse event or problem description, the event relationship to the test article or underlying condition, seriousness assessment, whether the event was anticipated or unanticipated, type of report (initial or follow-up), date of injury, whether the intervention was stopped, and, if so, whether it was re-started, and whether the event provides new risk information that alters the risk-benefit assessment and/or should be added to the informed consent disclosure.

11. PATIENT RECRUITMENT AND INFORMED CONSENT

11.1 Informed Consent

Informed consent: The Informed Consent form will be reviewed and approved by the local IRB at UPMC. The informed consent process will be completed per each site(s) Standard Operating Procedures (SOP). The primary purpose of the consent process is to protect the rights, safety, and welfare of human subjects. The consent process consists of: 1) sharing information, 2) active communication, 3) education, 4) building trust and rapport. The consent process will be conducted in accordance with:

- Title 21 CFR 50.20 - General Requirements for Informed Consent
- Title 21 CFR 50.23 - Exception from General Requirements
- Title 21 CFR 50.25 - Elements of Informed Consent
- Title 21 CFR 50.27 - Documentation of Informed Consent

- Title 21 CFR 50.40, 50.42, 50.44, 50.46, 50.48 - Protections Pertaining to Investigators Involving Prisoners as Subjects.
- Title 45 CFR 46.116 - General Requirements for Informed Consent (when applicable)
- Title 45 CFR 46.117 - Documentation of Informed Consent (when applicable)
- ICH GCP Consolidated Guideline - Part 4.8 Informed Consent of Trial Subjects
- The Declaration of Helsinki

11.2 Withdrawal of Consent

Patients may withdraw from the study at any time. Patients should make every attempt to complete the study as specified. Investigators should encourage patient treatment compliance and adherence. All deviations from the planned treatment schedule will be documented.

12. Statistical Methods and Determination of Sample Size

12.1 Statistical

Design Design

This is a prospective, single-center, randomized parallel group study of the feasibility, safety and efficacy of

nebulized Revefenacin 175 μ g once per day and Formoterol 20 μ g twice per day (n=30) vs. a standard bronchodilator protocol with nebulized Albuterol and Ipratropium every 6 hours (n=30) over the 7-day treatment period. This study is not designed to detect any difference of the two treatment regimens in terms of overall or any specific AE incidence. Safety will be evaluated descriptively on the basis of AEs, side effects, vital signs, and vital status.

Study endpoints

For efficacy and safety endpoints refer to Section 10.1-10.3.

Baseline

Baseline factors will include demographic characteristics (age, sex, race), AECOPD duration and severity, current and past medicine use, baseline clinical factors and co-morbidities.

12.2 Null and Alternative Hypotheses

The objective of this trial is to evaluate the feasibility, safety and efficacy of nebulized Revefenacin 175 μ g once per day and Formoterol 20 μ g twice per day vs. a standard bronchodilator protocol with nebulized Albuterol and Ipratropium every 6 hours. It is not planned to test any statistical hypotheses with regard to any endpoints in a confirmatory sense. Hence, all p-values will be nominally interpreted and no adjustments for multiple testing will be made.

12.3 Randomization and Statistical Power

12.3.1 Randomization

Participating patients with AECOPD will be randomized 1:1 to either a standard bronchodilator protocol with nebulized Albuterol and Ipratropium every 6 hours or nebulized Revefenacin 175 μ g once per day and Formoterol 20 μ g twice per day. Each patient will have a single randomization number indicating the allocated treatment. The treatment assignments will be generated with the use of a pseudo-random-number generator with stratification for age groups (<50, 50-69, >70) that will be used to ensure balance of these factors in the numbers of subjects assigned to each of the two treatments. The allocation to

treatment arms will be according to a predetermined computer-generated randomization schedule

that will not be disclosed to the clinical investigators.

12.3.2 Sample Size

An a priori sample size calculation was conducted for purposes of having enough statistical power to detect any significant differences between the treatment arms, given that they exist in the population of interest. A small effect size ($f = 0.105$) based on a minimum clinically important difference (MCID) for Borg Dyspnea score of 2.0 (Crisafulli E 2010) was utilized in the calculation. Using the MCID-based effect size, an alpha value of 0.05, a beta value of 0.20, two (2) treatment arms, 14 within-subjects observations (Borg scale twice per day for 7 days), a correlation amongst repeated measures of 0.5, and a nonsphericity correction of 1.0, enrollment of a total of $n = 60$ patients would be needed to achieve adequate statistical power ($n = 30$ in each treatment arm).

12.4 Statistical Methods

The efficacy analyses and the summary of safety data will be based on all randomized patients that received at least one dose of study medication. Beyond this, the analysis will be conducted in an intention-to-treat fashion. Frequency and descriptive statistics will be performed to describe the study participants' demographic and clinical characteristics. The trial data will be checked and cleaned before statistical analysis is completed. Data missingness will be accounted for by comparing study participants with and without missing observations using between-subjects statistics (chi-square, t-test, ANOVA). In the event that significant

differences are found between the "missing" groups, imputation of the missing observations will be conducted using a maximum likelihood estimation technique. Normality of continuous distributions will be assessed using skewness and kurtosis statistics. If either statistic is above an absolute value of 2.0, then the normality assumption will be violated. Levene's Test of Equality of Variances will be used to check for the statistical assumption of homogeneity of variance. Baseline characteristics between the two exposure groups will be compared using between-subjects statistics, including independent samples t-tests (normal continuous variables), Mann-Whitney U tests (non-normal continuous variables), and Chi-square analyses (categorical variables). In the event that statistically significant differences are detected in baseline characteristics, those variables will be entered into multivariate regression analyses to account for those differences.

In general, safety analyses will be descriptive in nature. No hypothesis testing regarding safety-related factors is planned prospectively. AEs will be coded using the MedDRA coding dictionary. Standard summary tables will be produced to compare the incidence of AEs across the treatment groups. All events with an onset after the first dose of study medication up to a period of 30 days after the last dose of study medication will be assigned to the treatment period for evaluation. Vital signs will be also summarized descriptively.

Multiple regression models will be used to predict for normally distributed continuous outcomes (level of dyspnea as measured by the Borg scale). Statistical assumptions for multiple regression models (normality, linearity, homoscedasticity, multicollinearity, and autocorrelation) will be tested before interpretation.

Poisson or negative binomial regression models will be used to predict for count variables (total doses of bronchodilators, total doses of bronchodilators per hospital stay, number of rescue doses needed per day of hospital stay, number of patients needing to switch/change treatment regimen). Logistic regression models will be employed for categorical outcomes (failure of treatment, need for supplemental oxygen) to generate adjusted odds ratios (AOR) with 95% confidence intervals (95% CI). All regression models will be used to investigate the multivariate associations of pertinent demographic, clinical and treatment factors with feasibility-, safety- and efficacy-related outcomes. Statistical significance will be assumed at an alpha value of 0.05 and all analyses will be conducted using SPSS Version 25 (Armonk, NY: IBM Corp.).

13. STUDY MANAGEMENT

The PI and study team has the site resources, time availability, and the patient population needed to complete this protocol under FDA, ICH, and GCP guidelines within the defined study timeline. Research that is subject to regulation, as defined in 46.102, must be reviewed and approved, by an institutional review board (IRB) that operates in accordance with regulation requirements of this policy. Per 21 CFR part 50 Investigator must obtain legal informed consent if human participants are being included within research and meet certain guidelines.

The PI is ultimately responsible for the conduct of the trial; however, he will delegate authority to appropriate members of the research team. The PI will ensure the following:

- Study team complies with be GCP and other regulatory requirements.
- The study team allows monitoring and auditing regulating institutions and sponsors.
- Ensures person delegated trial responsibilities are qualified and trained appropriately.
- Ensure that study team members have sufficient time to properly conduct and complete the trial within the agreed trial period.
- Ensure that all persons assisting with the trial are adequately informed about the protocol, the investigational product, and their trial-related duties and functions.
- Ensure record keeping and record retention of Financial Disclosure by Clinical Investigators is required in accordance with 21 CFR 50.
- Ensures compliance with, GCP guidelines and FDA regulatory requirements.
- Will maintain a list of research team members and delegated duties.
- Assures protocol compliance.
- Reports protocol non-compliance appropriately.
- Obtains IRB approval of the trial.
- Followings regulations and guidelines to protect subject rights, safety, and welfare.
- Controls the accountability of the investigational product(s).
- Ensures accurate case histories and records all observations and other data pertinent to the clinical trial on each subject.
- Disclosures of applicable conflicts of interest.
- Assures compliance by all research team members of GCP regulations

13.1 Data Documentation

Data will be documented on CRFs. The Investigator will retain all records related to the study in compliance with U.S. FDA regulations and ICH Good Clinical Practice Guidelines.

13.2 Data Storage

Data collected during the study will be retained in patients' research records for at least 6 years after the study is completed. At that time, the research information not already in the patients' medical records will be destroyed, per institutional guidelines. Any research information entered into a patient's medical record during the study will be kept indefinitely.

13.3 Data Protection

The trial will be carried out in compliance with the protocol, the principles laid down in the Declaration of Helsinki, version as of October 1996 (as long as local laws do not require to follow other versions), in accordance with the ICH Harmonised Tripartite Guideline for GCP. Standard medical care (prophylactic,

diagnostic and therapeutic procedures) remains in the responsibility of the treating physician of the patient. The PI will inform the sponsor immediately of any urgent safety measures taken to protect the study subjects against any immediate hazard, and also of any serious breaches of the protocol/ICH GCP. The rights of the investigator, of trial site, and of the sponsor with regard to publication of the results of this trial are described in the investigator contract.

Throughout the study, measures to ensure the privacy of information on study subjects will be maintained. All project investigators and staff have been certified for training in the use of human subjects in research and have received training in the new HIPAA regulations. Subjects and staff will be informed of the confidentiality of information and assured that data will be used only for statistical purposes and group analyses in which the individual cannot be identified. No data beyond what is stated in the informed consent will be sought without authorization from the subject or next of kin. Information on illnesses and hospitalizations will not be sought from hospitals or doctors without a signed medical release from the subject. Conversely, no information on any individual will be released to anyone other than project personnel without a signed medical release from the subject, or where appropriate, the next of kin or a physician in case of a life-threatening emergency to the subject. All project personnel will be instructed not to discuss any cases with persons other than project personnel.

All subjects will have assigned code numbers. All completed forms will be kept in locked files in locked rooms to which only project personnel have access. In addition to measures to ensure confidentiality is not breached from the use or storage of hard copies (discussed above), electronic files will be available to only key study personnel only on the server and designated PCs. Both the computers and the electronic files will be username/password protected. PCs will be kept in locked rooms. Server computer security is maintained 24 hours a day. The server is HIPAA compliant and will be used to back-up data from the laptop.

13.4 Data Confidentiality

Study subjects will not be identified by personal information. Each subject will be assigned a study number and this number along with their initials will be used on all study documents. Any personal information will be stored in a locked cabinet, access to which will be available only to the study team.

13.5 Data and Safety Monitoring

Monitoring will include review of original case records and Case Report Forms (CRFs), and will include monitoring to assess facilities and equipment, recruiting, record-keeping, protocol adherence, and data collection. The Investigator will record all protocol deviations. Unexpected clinically significant adverse events will be reported to the IRB. In general, the investigators will monitor any adverse reaction to the questionnaires and assessments conducted during the study. Any missing data will be omitted from the final statistical analysis.

13.6 Protocol Deviations

A protocol deviation is failure to follow procedures specified in the approved research protocol, which include (but are not limited to), deviations from study inclusion/exclusion criteria, or failure to follow criteria for subject follow-up, withdrawal, or timely monitoring procedures. Protocol deviations must be reported to the IRB by the PI *within 5 working days* from the day the investigator becomes aware of the event.

Protocol deviation reports to the IRB must include the subject identifier, date of deviation, impact on the subject's safety, and the plan for preventing the deviation in the future (if applicable).

13.7 Data Quality Assurance

A quality assurance audit/inspection of this trial may be conducted by the sponsor or sponsor's designees or by the overseeing IRB or by regulatory authorities. The quality assurance auditor will have access to all medical records, the investigator's trial-related files and correspondence, and the informed consent documentation of this clinical trial.

13.8 RECORDS

13.8.1 Source Documents

Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the investigator's site. Data entered in the eCRFs that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. For eCRFs all data must be derived from source documents.

13.8.2. Direct Access to Source Data and Documents

The PI will permit trial-related monitoring, audits, IRB review and regulatory inspection, providing direct access to source data/documents.

13.8.3 Storage of Records

The PI will retain the source documents and essential documents for a period of at least 3 years after the research is completed and the study is closed with the IRB. Records will be kept longer if other requirements apply.

13.9 Completion of Trial

When the trial is completed, the PI will inform the IRB and sponsor of the completion in writing.

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