## 1) Protocol Title

*An Investigator Initiated, Randomized, Double Blind, Placebo Controlled, Two Period, Crossover Study to Assess the Effect of BEVESPI AEROSPHERE ® Therapy* (Glycopyrrolate/Formeterol) *on Exercise Tolerance and Dynamic Hyperinflation in Patients with Chronic Obstructive Pulmonary Disease.*

## 2) HSC Review History

*N/A*

## 3) Investigators

William Stringer, M.D. Principal Investigator
Richard Casaburi, Ph.D., M.D. Co-Investigator
Harry B. Rossiter, Ph.D. Co-Investigator
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## 4) Objectives*

Patients with chronic obstructive pulmonary disease (COPD) have obstruction to expiratory airflow, marked breathlessness, high dyspnea scores, and reduced exercise tolerance relative to age and gender matched non-smoking controls (Casaburi, 2009; Casaburi et al., 2014; Puente-Maestu et al., 2016). A prominent mechanism for exercise intolerance is thought to be dynamic hyperinflation during exercise (an increase in the end-expiratory lung volume) that contributes to the sensation of breathlessness, and ultimately results in early cessation of exercise. A co-maladaptive mechanism of exercise limitation in COPD is related to wasted or excessive ventilation at all work intensities from increased dead space ventilation relative to total ventilation (increased $V_D/V_T$). This requirement for additional ventilation limits exercise capacity and contributes to dynamic hyperinflation and ventilatory limitation (O'Donnell et al., 2004).

Treatment with individual bronchodilators, including short acting beta agonists (SABA), long acting beta agonists (LABA), short acting muscarinic antagonists (SAMA) and long acting muscarinic antagonists (LAMA) is effective in partially reversing the expiratory airflow obstruction at rest and during exercise resulting in reduced dynamic hyperinflation. Because beta-agonists and anticholinergics broncho-dilate synergistically, they are often used in combination products (SABA+SAMA or LABA/LAMA). The optimal sustained bronchodilation effect in COPD appears to be achieved by fixed dose, long acting combination medications (LABA/LAMA). (Bateman et al., 2014; Casaburi, 2009; Casaburi et al., 2014; Cope et al., 2013; Huisman et al., 2015). As dynamic hyperinflation appears to also be a limiting factor in exercise tolerance, and LABA/LAMA preparations improve airflow during exercise, it appears likely that use of a fixed-dose combination bronchodilator,

BEVESPI AEROSPHERE ® (Glycopyrrolate/Formeterol) will increase exercise tolerance and reduce hyperinflation in COPD patients.

*We hypothesize that exercise tolerance in a constant work rate, high intensity cardiopulmonary exercise test will be increased with BEVESPI AEROSPHERE ® (Glycopyrrolate/Formeterol), and that the increase in exercise tolerance will be mediated by a combination of: 1) reduced dynamic hyperinflation, and 2) decreased dead space ventilation ($V_D/V_T$) during exercise.*

*Primary objective*: To determine the magnitude of exercise time improvement (seconds) with BEVESPI AEROSPHERE ® (Glycopyrrolate/Formeterol) relative to placebo during high intensity, constant work rate exercise in COPD patients.

*Secondary objective*: To determine if the $V_D/V_T$ can be reliably assessed during constant work rate exercise using transcutaneous $CO_2$ measurement ($tcpCO_2$) and, if so, if BEVESPI AEROSPHERE ® (Glycopyrrolate/Formeterol) results in a reduction in $V_D/V_T$ relative to placebo at isotime during high intensity constant work rate exercise in COPD patients.

*Tertiary objective:* To determine if computerized assessment of the spontaneous expiratory flow-volume loop during exercise can provide additional information about both dynamic hyperinflation and the effects of BEVESPI AEROSPHERE ® (Glycopyrrolate/Formeterol) during high intensity, constant work rate exercise in COPD patients.

## 5) Background*

Chronic obstructive pulmonary disease (COPD) is a major worldwide cause of disability and death, with an estimated prevalence of 210 million and with more than 80 million of these having severe disease (World Health Organization). Recent data suggest that COPD is now the third leading cause of death in the USA (Miniño, 2010). In addition, COPD is among the top five causes of adult disability, of which exercise intolerance consequent to dynamic hyperinflation is the main feature (Eisner et al., 2011), (Casaburi and ZuWallack, 2009).

In COPD patients, exertional dyspnea causes the avoidance of physical activity (Casaburi et al., 1999). Relief of hyperinflation, as well as reduction in wasted ventilation and reduction in $V_D/V_T$ should result in improved exercise capacity.

The purpose of the proposed study is to determine if exercise tolerance in COPD patients is improved with the use of FDA approved (https://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.DrugDetails) BEVESPI AEROSPHERE ® (Glycopyrrolate/Formeterol) relative to placebo during a high intensity, constant work rate cardio-pulmonary exercise test.

We hypothesize that this LABA/LAMA preparation, BEVESPI AEROSPHERE ® (Glycopyrrolate/Formeterol) relative to placebo will demonstrate improved pulmonary function and reduce dynamic hyperinflation in COPD patients in a stable phase of their disease.

An advantage of BEVESPI AEROSPHERE ® (Glycopyrrolate/Formeterol) is related to the pressurized metered dose inhaler delivery system. All other LABA/LAMA formulations (either once or twice a day) are dry powder or soft mist inhalers, which may be more difficult for patients to utilize on a regular basis and to self-administer the appropriate dosage each time.

*Use of Constant Work Rate (Endurance) Tests to evaluate exercise capacity in COPD*

Puente-Maestu, et al. have recently reviewed the literature on the use of exercise testing in the evaluation of the efficacy of interventions for the European Respiratory Society (ERS). (Puente-Maestu et al., 2016) This official Task Force Statement concludes that "Exercise tests are reliable and consistently responsive to rehabilitative and pharmacological interventions." and that "While bronchodilators do not always show clinically relevant effects in chronic obstructive pulmonary disease, high-intensity constant work rate (endurance) tests (CWRET) are considerably more responsive than incremental exercise tests and 6 minute walk test (6MWTs)." These authors document that, in their exhaustive review of the literature, a minimally important clinical difference (MCID) in the CWRET in COPD was 105 seconds (page 434, Table 3). Further, for single long acting bronchodilator interventions in COPD, 14/26 studies (54%) showed an average improvement in exercise duration of > 105 seconds or a relative percentage increase in time of 33% (page 435, Table 4). For non-pharmacologic interventions (e.g. rehabilitation, Heliox, Oxygen, Non-Invasive Ventilation (NIV), etc.) a change in endurance time of 105 seconds or a percentage increase in time of 33% was suggested as the MCID (page 437, Figure 1).

We have therefore selected constant work rate (endurance) tests on a cycle ergometer to evaluate the exercise capacity improvements in COPD with the BEVESPI AEROSPHERE ® (Glycopyrrolate/Formeterol) combination. Patients will perform an initial incremental test to exhaustion (Wasserman et al., 2005), and this will be followed (in about 2 hours) with a constant work rate exercise test (CWRET) at 80 % of the peak work rate targeting an exercise duration between 4 and 8 minutes (van der Vaart et al., 2014) .

*$V_D/V_T$ Measurement using Transcutaneous $CO_2$ during Exercise*

Measurement of physiologic dead space to tidal volume ratio ($V_D/V_T$) is an important measure of gas exchange efficiency. $V_D/V_T$ is the fraction of the expired tidal volume that does not participate in gas exchange (specifically, in $CO_2$ elimination). In health, $V_D/V_T$ is

~0.3 at rest and decreases during exercise. $V_D/V_T$ is immediately reduced on initiation of exercise and at low exercise intensity, and then remains approximately constant as exercise intensity increases (Jones et al., 1966; Wasserman et al., 1967; Hansen et al., 1984; Lewis et al., 1994; Sun et al., 2002; Wasserman et al., 2012). In diseases affecting the lungs or blood flow through the lungs (in particular) $V_D/V_T$ can be high at rest (>0.3), but most notably $V_D/V_T$ fails to fall substantially during exercise, thereby contributing to functional limitations in these patients – limits that reduce the quality of life, and increases morbidity and mortality. Therefore, exercise unmasks clinically meaningful abnormalities in $V_D/V_T$. The normal exercise-induced decrease $V_D/V_T$ is the result of processes that influence both $V_D$ and $V_T$ independently. Early in exercise, alveolar dead space decreases as pulmonary arterial pressure increases and apical lung units become perfused. Anatomic dead space volume increases mildly during exercise as volume of the conducting airways increase due to exercise-induced bronchodilation and increased radial traction on airways at higher lung volumes. At high exercise intensities, an increase in the ratio of ventilation to perfusion (VA/Q) may also occur (Wagner et al., 1986). Each of these processes contribute to increasing $V_D$ during exercise. However, these effects are relatively small compared to the large increase in tidal volume, resulting an overall VD/VT reduction in healthy individuals as exercise intensity is increased (ATS/ACCP, 2003). Patients with chronic diseases of the lungs or cardiovascular system often have an elevated $V_D/V_T$ at rest and an abnormal exercise response where $V_D/V_T$ fails to fall, or even increases. Examples of diseases where this pattern of exercise response is seen includes: emphysema, COPD, asthma, pulmonary fibrosis, pulmonary vascular disease, right or left ventricular dysfunction, and ischemic heart disease (Wasserman et al., 2012). This may occur because of a high alveolar dead space i.e. alveoli that are not perfused, a worsening of VA/Q mismatch on exercise or a small (limited) exercise-induced increase in $V_T$. As such, knowledge of $V_D/V_T$ during exercise provides valuable insight into the etiology of a patient's pathophysiology.

$V_D/V_T$ is calculated from the equation: $V_D/V_T = (PaCO_2 – P_ECO_2) /(PaCO_2)$ (1) where $PaCO_2$ is the partial pressure of carbon dioxide ($CO_2$) in the arterial blood and $P_ECO_2$ is the mixed expired $PCO_2$. Since, by definition, $P_ECO_2$ is the inverse of the ratio of the expired ventilation ($V_E$) to the $CO_2$ output ($VCO_2$), $V_D/V_T$ can be calculated from the relation: $V_E/VCO_2 = 863 / [PaCO_2 \cdot (1 - V_D/V_T)]$ (2) where a high value for $V_E/VCO_2$ is considered as a possible indication of a high $V_D/V_T$. This approach is commonly used in clinical exercise testing because standard metabolic cart equipment measures directly both $V_E$ and $VCO_2$ on a breath-by-breath basis.

However, elevated $V_E/VCO_2$ may be attributed to: (1) an increased $V_D/V_T$; (2) a decrease in $PaCO_2$; or (3) both, such that the relationship between $V_E/VCO_2$ and $V_D/V_T$ is not simple (Figure 1). Factors related to altered respiratory control, such as hyper- or hypo-ventilation due to anxiety, hypoxemia, chronic respiratory alkalosis, metabolic acidosis, or altered respiratory mechanics may cause changes in $PaCO_2$ that alter $V_E/VCO_2$ independently of $V_D/V_T$. These assumptions become especially pertinent in pulmonary pathologies where gas exchange and $CO_2$ elimination are impaired.

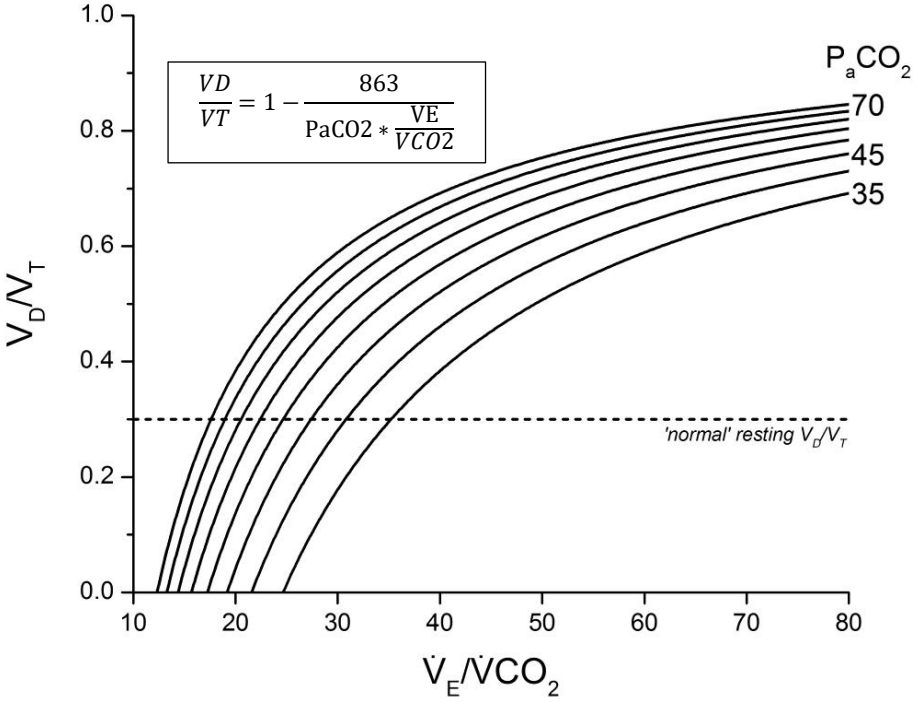


Figure 1. The relationship between deadspace fraction of tidal volume ($V_D/V_T$) and the ventilatory equivalent for $CO_2$ ($V_E/VCO_2$) across a range of different arterial $PCO_2$ ($PaCO_2$) values. The equation in the insert is a rearranged form of Eq (2) above.

In line with this, we have recently shown (Roman et al., 2013), in the largest collection (n=691) of cardiopulmonary exercise tests with serial arterial blood gas measurements, that $V_E/VCO_2$ (using the $V_E/VCO_2$ value at the lactate threshold (LT) during exercise) is inadequately discriminatory of abnormalities in the $V_D/V_T$ response. In this population of patients with a wide range of diagnoses, while very high (>39) or very low (<28) $V_E/VCO_2$ values were indicative of abnormal or normal $V_D/V_T$ respectively. In 58% of these exercise tests the $V_E/VCO_2$ value was between these limits and provided no reliable information on $V_D/V_T$. Again, this emphasizes that accurate diagnosis of $V_D/V_T$ pathology in a large majority of patients requires direct measurement of $PaCO_2$. Recently, in a preliminary study we have shown that using $tcpCO_2$ as a surrogate of $PaCO_2$ in the above equation gives a better estimate of dead-space ventilation. (Cao et al.)

In the ideal lung, ventilation is evenly matched to perfusion and gas exchange is highly efficient. Patients with COPD have abnormal $V_D/V_T$ responses to exercise in that they demonstrate an increase in $V_D/V_T$ due to non-uniform emptying of the airways, with the longest time-constant low VA/Q lung units contributing to end tidal gas (Hansen et al., 2007). There is opportunity, therefore, to dramatically improve the assessment of a pathological $V_D/V_T$ response to exercise using non-invasive transcutaneous $PCO_2$ measurement ($tcPCO_2$), as an accurate and precise surrogate for $PaCO_2$. This method determines the $PCO_2$ of skin capillaries under a heated, Severinghaus-type electrode. The sensor is clipped to the earlobe and mildly heats the skin and dilates the underlying

capillaries; this increases the gas diffusion through the lipid structure of the skin, allowing carbon dioxide diffuse to the electrode for measurement. Because the metabolic rate in the ear is low, the resulting increase in blood flow causes capillary $PCO_2$ to approach $PaCO_2$. Were $tcPCO_2$ to approximate $PaCO_2$ change during an exercise test in patients with COPD, it could provide a considerable advance in the diagnostic capability of cardiopulmonary exercise testing.

We have identified 20 published articles where $tcPCO_2$ has been used during cardiopulmonary exercise testing (Table 1). Of the 20 articles, 3 are noteworthy (Carter and Banham, 2000; Sridhar et al., 1993; Stege et al., 2009) in that they made paired arterial and transcutaneous PCO2 measurements during clinical exercise assessments in patients. Sridhar et al. (1993) found good limits of agreement between $PaCO_2$ and $tcPCO_2$ during cycling ergometry (mean bias 0.2 mm Hg; CI -1.2 to +1.9 mm Hg) in 24 patients with chronic obstructive pulmonary disease (COPD), ischemic heart disease (IHD) and other pulmonary disorders.

Carter and Bahnam (2000) were the first to perform rapid arterial blood sampling (every 2 minutes) during a standard clinical cardiopulmonary exercise test in 14 patients with COPD, IHD and other cardiac and respiratory disorders. They found very good limits of agreement between arterial and transcutaneous measurements (mean bias 0 mm Hg; CI -0.2 to +0.2 mmHg). However, they used an "in vivo" calibration method where the $tcPCO_2$ values were corrected using a resting arterial blood PaCO2 measurement prior to the exercise test. A major potential benefit of non-invasive $tcPCO_2$ measurement is to avoid the requirement for arterial blood sampling. Therefore, the in vivo calibration approach used by Carter and Bahnam (2000) would be an undesirable recommendation for standard use.

**Table 1.** Publications reporting transcutaneous $PCO_2$ measurement during exercise

| | Authors | Year | Population | n | Ergometer | $P_aCO_2$[2] | $V_D/V_T$[3] | Comments |
|---|---|---|---|---|---|---|---|---|
| 1 | Kentala *et al.* | 1984 | Patients[1] | 113 | Not available | **Yes** | No | $P_aCO_2$ at maximum exercise |
| 2 | Nickerson et al. | 1984 | Healthy | 9 | Cycle | No | No | |
| 3 | Ewald *et al.* | 1985 | Healthy | 17 | Not stated | No | No | |
| 4 | Steinacker *et al.* | 1987 | Healthy | Not available | Treadmill | **Yes** | No | $P_aCO_2$ every 2-5 minutes |
| 5 | Hoffmann *et al.* | 1990 | Healthy | 9 | Cycle | **Yes** | No | $P_aCO_2$ at moderate steady-state |
| 6 | Breuer *et al.* | 1990 | Healthy | 23 | Not available | **Yes** | No | Full article not available |
| 7 | Nixon *et al.* | 1990 | Cystic Fibrosis | 36 | Cycle | No | No | |
| 8 | Stanghelle *et al.* | 1993 | Cystic Fibrosis | 12 | Cycle | **Yes** | No | $P_aCO_2$ at rest, exercise, recovery |
| 9 | Sridhar *et al.* | 1993 | Patients[1] | 24 | Cycle | **Yes** | No | $P_aCO_2$ every 1 minute No $P_{ET}CO_2$ |
| 10 | Breuer *et al.* | 1993 | Healthy | 15 | Cycle | No | No | |
| 11 | Keilty *et al.* | 1994 | COPD | 8 | Treadmill | No | No | |
| 12 | Liu *et al.* | 1995 | Healthy | 11 | Cycle | No | No | |
| 13 | Carter *et al.* | 2000 | Patients[1] | 20 | Cycle | **Yes** | **Yes** | $P_aCO_2$ every 2 minutes No $P_{ET}CO_2$ '*In vivo* $tcPCO_2$ calibration' |
| 14 | Planés *et al.* | 2001 | Lung disease | 81 | Treadmill | **Yes** | No | $P_aCO_2$ at rest and maximum |
| 15 | Holmgren *et al.* | 2001 | Post cardiac surgery | 1 | Not stated | No | No | |
| 16 | Marcus *et al.* | 2002 | Cystic Fibrosis Controls | 22 21 | Treadmill Treadmill | No No | No No | |
| 17 | Carter *et al.* | 2006 | Transplant patients | 47 | Cycle | No | No | |
| 18 | Stege *et al.* | 2009 | Patients[1] | 21 | Cycle | **Yes** | No | $P_aCO_2$ every 3 minutes |
| 19 | Ouedraogo *et al.* | 2011 | Claudication | 778 | Treadmill | No | No | |
| 20 | Porszasz *et al.* | 2013 | COPD | 14 | Cycling | No | No | |

[1] 'Patients' are sequential referrals to cardiopulmonary exercise testing for unexplained dyspnea
[2] $P_aCO_2$ indicates whether arterial $PCO_2$ was measured
[3] $V_D/V_T$ indicates whether $V_D/V_T$ was calculated

Stege et al. (2009) performed the most detailed investigation to date in 21 patients with COPD, asthma, sarcoidosis and other respiratory disorders. They showed that tcPCO2 provided a superior $PaCO_2$ estimate (mean bias -0.2 mm Hg; CI -5.7 to 5.2 mm Hg) compared with end-tidal $PCO_2$ (mean bias 7.7 mm Hg; -0.67 to 16.2 mm Hg).

We have recently performed a study in our laboratory (which is in manuscript preparation) of 10 COPD patients using the Radiometer (TOSCA 500) Transcutaneous $pCO_2$ device and compared the non-invasive results to multiple simultaneous arterial blood gas $pCO_2$ values from an arterial line during ramp pattern exercise. We have found that across a wide range of $PaCO_2$ from < 30 torr to > 50 torr, the transcutaneous $pCO_2$ was accurate and precise relative to the arterial $pCO_2$ value (See Figure 2, Bland Altman analysis, below). Specifically, the bias was very nearly zero and the standard deviation was about 2 torr. We believe that this device will allow us to accurately and precisely assess repetitive VD/VT measurements during exercise to assess the effect of the *BEVESPI AEROSPHERE ®* (Glycopyrrolate/Formeterol) on airflow and hyperinflation as well as the effect on deadspace ventilation (VD/VT).

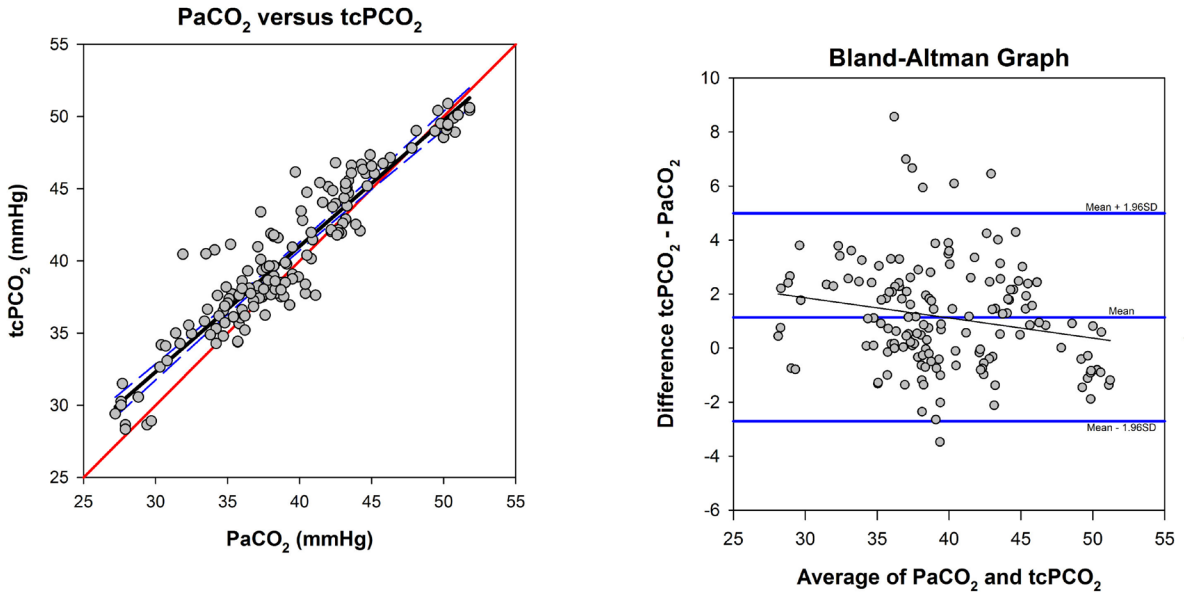


Figure 2. Bland – Altman analysis of arterial $CO_2$ ($PaCO_2$) versus transcutaneous $CO_2$ ($tcPCO_2$) during exercise in 10 COPD patients.

The effect of bronchodilators on exercise gas exchange efficiency, as quantitated by $V_D/V_T$, has not received adequate study in COPD patients (Díaz et al., 2001; Elbehairy et al., 2015; Marvin et al., 1983; O'Donnell et al., 2016). Physiologic considerations would predict that bronchodilators would have three distinct effects on $V_D/V_T$. First, bronchodilation of airways increases dead space in the conducting zone of the lung. Second, bronchodilation of airways serving poorly perfused regions of the lung has potential to increase physiologic dead space, leading to $V_D/V_T$ increase. Third, bronchodilation tends to reduce dynamic hyperinflation, which allows a slower deeper breathing pattern, allowing a greater tidal volume and/or an attenuated constraint of tidal volume increase during exercise. Better maintenance, or increase, in tidal volume without change in dead space volume would translate into a lesser $V_D/V_T$. In fact, mildly greater isotime inspiratory capacity and pulmonary ventilation has been observed in COPD during exercise following bronchodilator therapy (O'Donnell et al., 2004). It is not possible to determine whether this stems from an increase in $V_D/V_T$ or a decrease in $PaCO_2$. This study will provide this information, yielding better understanding of the beneficial effects of bronchodilator therapy on the exercise responses of COPD patients.

We therefore feel that transcutaneous $pCO_2$ measurement will be an effective, non-invasive way to repetitively determine the effects of *BEVESPI AEROSPHERE ®* (Glycopyrrolate/Formeterol) on $V_D/V_T$ during exercise.

*Flow-Volume Measurement During Exercise*

Breath-by-breath quantification of progressive airflow limitation during exercise in COPD is an area in which this laboratory has substantial experience. We have published that the progressive fall in intrabreath flow, manifested by concavity in the spontaneous expiratory flow volume (SEFV) curve, can be analyzed electronically from the digitized expiratory flow signal (100 Hz). Each breath's SEFV curve, point of highest flow ($V_{max}$) and end-expiratory flow ($V_{EE}$) can be identified using a 'rectangle diagonal area' or (RAR) strategy. See Figure 3; RAR < 0.5 identifies concavity of the SEFV curve and identifies patients with progressive airflow limitation during exercise. (Ma et al., 2010) We have recently had a paper accepted for publication demonstrating a close correlation between the onset of concavity in the SEVF curve and dynamic hyperinflation.(Varga et al., 2016)

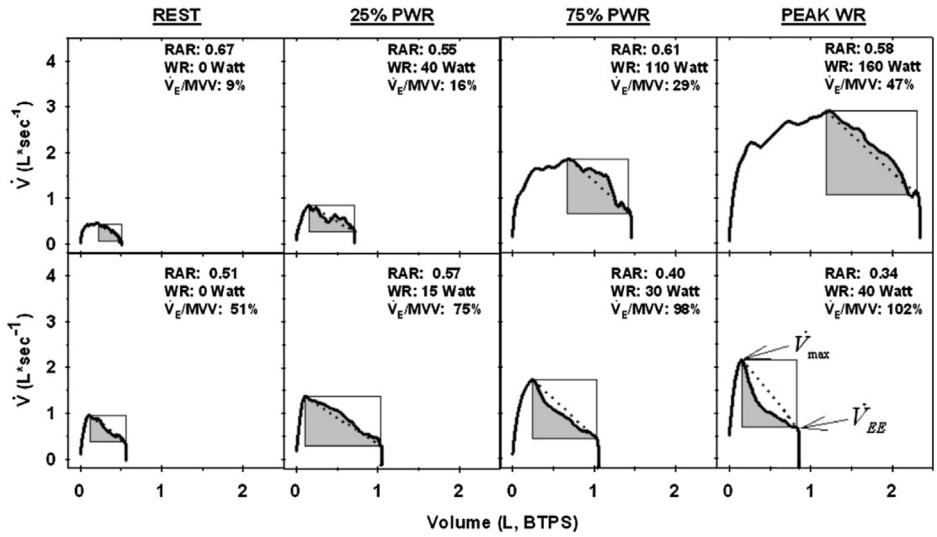


**Figure 3**: Progression of the spontaneous flow volume (SEFV) curve configuration during incremental exercise in a healthy subject (top panels) compared to a patient with COPD (lower panels).

Recently, Porszasz {Porszasz, 2013, Effect of tiotropium on spontaneous expiratory flow-volume curves during exercise in GOLD 1&2 COPD} has shown that tiotropium significantly increased RAR during exercise while improving dynamic hyperinflation and resting FEV1. (Porszasz et al., 2013) We therefore feel exercise flow-volume analysis to determine the change in RAR during exercise will add additional information regarding airflow improvements leading to less hyperinflation in patients treated with *BEVESPI AEROSPHERE ®* Therapy (Glycopyrrolate/Formeterol). We hypothesize that, in COPD patients, at an identical work rate and exercise time, RAR will be higher after treatment with this combination bronchodilator.

## 6) Setting of the Human Research

Patient recruitment and testing will take place at Los Angeles Biomedical Institute (LABioMed) in Torrance, California. Our research group is located in the Chronic Disease Clinical Research Center (CDCRC) building. There is adequate free parking and a large reception area for our research subjects. Our Pulmonary group consists of 4 principal investigators (Casaburi, Porszasz, Rossiter and Stringer), 5 study coordinators, several postdoctoral researchers, a full time exercise physiologist, and other technical research staff. The research space available to us in the CDCRC includes 5 separate rooms that house an exercise-training center, a complete exercise physiology laboratory with state of the art cardiopulmonary exercise testing equipment (including the ability to perform inspiratory capacity maneuvers during exercise), a Radiometer transcutaneous $CO_2$ monitor (TOSCA 500), the equipment to perform either cycle and treadmill exercise, a 6 minute walk course, and a complete pulmonary function laboratory with spirometry, body box and $D_LCO$. We also have 3 well-equipped examination rooms and offices suitable for obtaining informed consent, interviewing subjects, performing physical examinations, and discussing study specifics in a quiet, private, and protected environment.

## 7) Resources Available to Conduct the Human Research

This study is financially supported by AstraZeneca as part of their Investigator Initiated Studies program. The study design was initiated by the LA BioMed investigators.

The Pulmonary Division in the Chronic Disease Clinical Research Center (CDCRC) at LA BioMed has a > 20-year history in recruiting large numbers of COPD patients and healthy controls for multiple NIH, DOD, and industry sponsored clinical trials, including a large number of exercise studies. We commonly conduct large-scale COPD-related clinical trials, and as such there is potential access to several hundred subjects per year.

Fifty COPD subject/patient volunteers are needed for this study over an approximate 1-1.5 year period, which is a small fraction of our recruitment pool. We regularly enroll subjects into COPD exercise research studies, therefore, we do not anticipate any problems with patient recruitment. All of our investigators (Casaburi, Porszasz, Rossiter and Stringer) and research staff will contribute to the study. Because Dr. Casaburi has received consulting and speaking fees from Astra Zeneca a management plan for his potential conflict of interest (COI) is in place. He will disclose this COI to study staff and research participants. He will not engage in participant recruitment or the consent process, among other restrictions. All members of the research team have extensive experience in working with COPD patients in physiologic exercise studies. The methods used in this study were developed at LABioMed and the PI and all Co-Is are world leaders in the field, and contribute to setting the guidelines for clinical and research exercise testing in patient populations.

All the equipment required for the study is in standard use in our lab. The PI (Stringer) will devote 10% FTE to the study, with Co-PIs (Casaburi and Rossiter) will contribute 3% FTE. Co-I (Porszasz) will contribute 10% FTE. All investigators have MD or PhD degrees or both.

Recruitment and regulatory compliance will be supported by contributions from study coordinators (Cavanaugh, Diaz). Physiological testing will be supported by post-doctoral scientists, and an exercise physiologist lab (Calmelat). Staff members have been involved in previous studies using similar measurements and are well trained in their application. Our laboratory has weekly staff meetings where the experimental protocols and recruitment goals are continually reviewed and the current activities of each staff member reviewed.

No adverse events are anticipated. However, in the event of an adverse event, our lab is equipped with a crash cart and a California licensed physician will be available in the Exercise Laboratory during initial exercise tests for each subject. In case of medical emergency, the lab is located in the CDCRC Building on the Harbor-UCLA Medical Center (HUMC) campus, with excellent access to the emergency facilities. HUMC is a full service, academic medical center, a level 1 trauma center, and an STEMI receiving center for our region. All of the physician investigators are Harbor-UCLA physicians with full and unrestricted California medical licenses.

The principal investigator or our study coordinators will be providing complete information about the study and obtaining informed consent prior to initiation of the study. The principal investigator will be available for any subject questions through and after the study.

## 8) Prior Approvals

The approval and contracting process is underway between LABioMed with AstraZeneca (AZ). A detailed investigator initiated proposal has been submitted via the AZ website and has obtained tentative approval from the world research team. Final contracts are scheduled to be signed by late September 2016.

## 9) Study Design

### a) Recruitment Methods

Potential subjects for the study will be drawn from people known to our Pulmonary Research Group in the Chronic Disease Clinical Research Building (CDCRC) who have previously participated in our studies, attended clinics of Harbor-UCLA Medical Center, have completed a local Pulmonary Rehabilitation Program, are a member of a local patient support group, or have their clinical care performed in the network of area pulmonologists (including Kaiser and Health Care Partners). Subjects

who have given prior consent for contact will be contacted by phone to determine their willingness to participate, and if agreeable, will be invited to the study site for a complete in-person explanation of the protocol and consent.

Advertising (paper, internet, and radio) is not currently planned, however advertising may be utilized if the recruitment goals are not optimal 4 months after study initiation. If advertising is pursued, all advertising copy, media, and text will be approved by the LABioMed Institutional Review Board.

Subjects are reimbursed for their time and inconvenience in participating in this study. They will be informed of the following:

"For your time and inconvenience related to your taking part in this study, you will be paid a total of $1,250 if you complete this study. If you do not complete the study, for any reason, you will be paid for the study visits you do complete according to the following schedule: $300 for visit 1; $200 for visit 2; $150 for visits 3, 4, 5, 6, and 7."

## b) Inclusion and Exclusion Criteria*

***Inclusion criteria***

1) All patients must have a clinical diagnosis of chronic obstructive pulmonary disease (COPD) and must meet the following criteria:
   (a) Stable state of their disease with no exacerbation (antibiotics, oral steroids, ER visit, or hospitalization for COPD) within the previous 4 weeks; and
   (b) At visit 1 Spirometric Values must demonstrate a post-bronchodilator $FEV_1$ between 35% and 80% of predicted normal and a post-bronchodilator $FEV_1/FVC$ <70%. [The rationale for the lower limit is to exclude patients unlikely to tolerate withholding of long acting bronchodilators. The rationale for the upper limit is to exclude patients unlikely to be limited in their exercise tolerance by hyperinflation and air trapping.]
2) Male or female patients, between 40 and 80 years (inclusive) of age.
3) Patients must be current or ex-smokers with a smoking history of more than 10 pack-years.
4) Patients must be able to perform technically acceptable pulmonary function tests and a symptom-limited cardiopulmonary cycle ergometry test.
5) Patients must be able to inhale medication in an acceptable manner from the metered dose inhalers used in this study.

***Exclusion criteria***

1) Patients with a significant disease other than COPD; a significant disease is defined as a disease which, in the opinion of the investigator, may
   (i) put the patient at risk because of participation in the study,

(ii) influence the results of the study, or
(iii) cause concern regarding the patient's ability to participate in the study.

2) Patients with a documented personal history of childhood asthma, a clinical presentation consistent with asthma, and a family history of asthma. For patients with allergic rhinitis, atopy, or prior allergy treatment, medical records will be obtained to verify that the patient does not have asthma. The final determination on the possibility of an overlap condition [Asthma-COPD Overlap Syndrome, (Postma and Rabe, 2015)], and thus, appropriateness for entry into the study, will be the principal investigator's decision.
3) Patients with any of the following conditions:
   a) A history of myocardial infarction within 1 year of screening visit.
   b) Unstable or life-threatening cardiac arrhythmia.
   c) Hospitalized for heart failure within the past year.
   d) Known active tuberculosis.
   e) A malignancy for which patient has undergone resection, radiation therapy or chemotherapy within the past 6 months (patients with treated local skin tumors are allowed).
   f) A history of life-threatening COPD exacerbation requiring intubation.
   g) A history of cystic fibrosis.
   h) Clinically significant and active bronchiectasis.
   i) A history of alcohol or drug abuse within the past year.
   j) Any contraindications for exercise testing as outlined below (see contraindications to exercise).
   k) Patients who have undergone thoracotomy with pulmonary resection in the past year.
4) Patients being treated with oral corticosteroid medication at unstable doses (i.e., less than six weeks on a stable dose) or at doses in excess of the equivalent of 10 mg of prednisone per day or 20 mg every other day.
5) Patients who regularly use daytime oxygen therapy for more than 6 hours per day and in the investigator's opinion will be unable to abstain from the use of oxygen therapy during clinic visits and exercise testing.
6) Patients who desaturate to $S_pO_2$ <80% on screening incremental exercise testing.
7) Patients who have completed a pulmonary rehabilitation program in the six weeks prior to the screening visit or patients who are currently in a pulmonary rehabilitation program.
8) Patients who have a limitation of exercise performance as a result of factors other than fatigue or exertional dyspnea, such as arthritis in the leg, angina pectoris or claudication or morbid obesity.
9) Patients with a constant power cycle ergometry endurance time less than 4 or greater than 8 minutes after work rate adjustment procedures (described below).
10) Patients who have taken an investigational drug within one month or six half-lives (whichever is greater) prior to screening visit (Visit 1).
11) Pregnant or nursing women.
12) Women of childbearing potential who are not using a highly effective method of birth control. Female patients will be considered to be of childbearing potential unless surgically sterilized by hysterectomy or bilateral tubal ligation, or post-menopausal for at least two years. Pregnancy testing will be performed in women of childbearing potential

and repeated during the study if questioning of the participant suggests a change of status.

13) Patients who are currently participating in another interventional study.
14) Patients who are unable to comply with pulmonary medication restrictions (washout of any LABA/LAMA) prior to randomization.

All subjects will be screened for eligibility during visit 1. Eligibility will be determined by medical history, physical examination, spirometry (visit 1) and exercise testing (visit 1). Women with the potential for pregnancy will be tested using a urine-based testing kit. Eligibility will be determined according to the study inclusion and exclusion criteria

## c) Local Number of Subjects

Fifty patients are required to complete the research procedures. LA BioMed is the only study site. Based on our experience we anticipate an approximate 15% screen failure rate from spirometry and a 15% screen failure rate following the screening ramp exercise test and subsequent constant work rate exercise test. Therefore, we anticipate screening approximately 70 patients to complete the research in 50 subjects.

## d) Study-Wide Number of Subjects*

Not applicable.

## e) Study Timelines*

Each patient will be enrolled for approximately 12 weeks. This is a randomized, crossover, placebo controlled, two-period, double-blind study that includes 7 laboratory visits and two, 2 week washout periods from drug or placebo.

The timeline for each patient visit is shown in Figure 4. Visit 1 will be approximately 1 hour duration. Visit 2 will be approximately 4 hours duration. Visits 3, 4, 5, and 6 will each be approximately 2 hours duration. Visit 7 will take < 1 hour.

Completion of study of the patient population (n=50) is anticipated to take 12 - 18 months. Depending on protocol, IRB and contract approval a tentative target for starting patient recruitment is December 2016. Completion of primary analysis is anticipated within three months of the last patient completing the protocol.

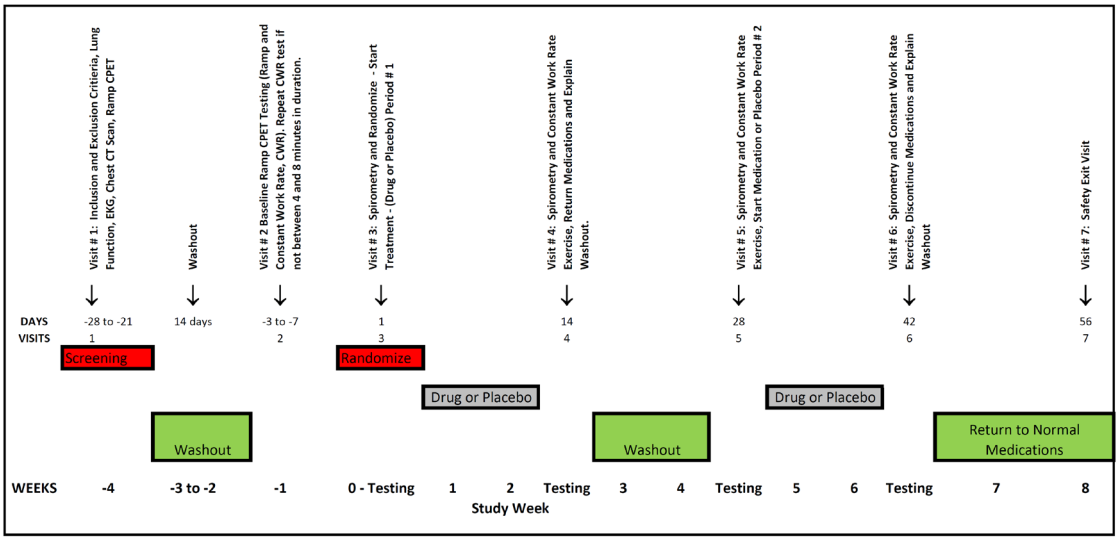


**Figure 4.** Study Timeline for weeks -4 to 8. Screening, Washout, Randomization, 2 week Drug or Placebo periods, Ramp Pattern and Square Wave Exercise Testing, and Safety Visit at day # 56. Drug refers to BEVESPI AEROSPHERE ® Therapy (Glycopyrrolate / Formeterol). The administration of these drugs (drug or placebo) will be double-blinded.

Our group anticipates that the performance of the entire study from first enrollment (subject # 1) to completion (subject # 50) will require between 12 and 18 months.

## f) Study Endpoints*

The study endpoint is completion of Visit # 7. Patient safety will be monitored throughout, and the procedures stopped if a problem arises. There are no clinical or therapeutic endpoints.

Safety endpoints include the ability to complete a ramp and constant work rate exercise test safely, as judged by the investigator. Exercise tests will be stopped if clinically significant changes in the ECG occur, such as ST-segment depression, marked desaturation (< 80%), or a dangerous/complex/progressively increasing arrhythmias.

**Definition of adverse events**

An adverse event is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (eg, nausea, chest pain), signs (eg, tachycardia, enlarged liver) or the abnormal results of an investigation (eg, laboratory findings, electrocardiogram). In clinical studies, an AE can include an undesirable medical

condition occurring at any time, including run-in or washout periods, even if no study treatment has been administered.
The term AE is used to include both serious and non-serious AEs.

**Definitions of serious adverse event**

A serious adverse event is an AE occurring during any study phase (ie, run-in, treatment, washout, follow-up), that fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
- Is a congenital abnormality or birth defect.
- Is an important medical event that may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above.

The causality of SAEs (their relationship to all study treatment/procedures) will be assessed by the investigator(s) and communicated to AstraZeneca.

**Causality assessment**

The Investigator will assess causal relationship between Investigational Product and each Adverse Event, and answer 'yes' or 'no' to the question 'Do you consider that there is a reasonable possibility that the event may have been caused by the investigational product?'

For SAEs a causal relationship will also be assessed for other concomitant medications, study procedures, and comparator study drugs. Note that for SAEs that could be associated with any study procedure the causal relationship is implied as 'yes'.

Adverse events (AE) and serious adverse events (SAE) are safety endpoints of the study. Medical judgment will be used to determine the relationship between study drug or procedures and an (S)AE, considering all relevant factors, including pattern of reaction, temporal relationship, de-challenge or re-challenge, confounding factors such as concomitant medication, concomitant diseases and relevant history.

Changes in vital signs, ECG, physical examination and laboratory test results will be recorded as an (S)AE, if they are judged clinically relevant by the investigator. Vital signs, ECG, and physiological test results are recorded as part of cardiopulmonary exercise testing at each visit. These may cause exclusion of the patient from the study at any time, should they meet the exclusion criteria listed.

## g) Procedures Involved in the Human Research*

All study procedures are done solely for the purposes of research.

***Study design***

This will be a randomized, placebo controlled, double-blind study investigating the effects of the FDA approved fixed combination long acting beta agonist and long acting muscarinic antagonist (LABA/LAMA) inhaler BEVESPI AEROSPHERE ® (Glycopyrrolate/Formeterol) on Exercise Tolerance and Dynamic Hyperinflation in Patients with Chronic Obstructive Pulmonary Disease.

The study is a crossover, within-patient, two period design comparing the effect BEVESPI AEROSPHERE ® Therapy (Glycopyrrolate/Formeterol) to placebo on endurance time (exercise capacity/time during a constant work rate exercise test), dynamic hyperinflation, and dead space to tidal volume ($V_DV_T$). Fifty (50) patients with moderate to severe COPD (post-bronchodilator $FEV_1$ between 35% and 70% of predicted normal and a post-bronchodilator $FEV_1$/FVC <70%) will be recruited into this study.

Initially pulmonary function, chest computerize tomography (CT) imaging, and cardiopulmonary exercise variables will be used to characterize recruited patients. Subsequently, a constant power exercise test (calculated from the initial incremental exercise test to bring the patient to intolerance to between 4 and 8 minutes on a constant work rate exercise test) will be designed and administered at the same work rate for the entire study. Patients will perform two tests, each to the limit of tolerance, while being treated with either BEVESPI AEROSPHERE ® (Glycopyrrolate/Formeterol) bronchodilator and placebo. A two week wash out period will precede randomization and after the first treatment period. The patient will return to their usual medications at day 42 and will have a final exit/safety visit at study completion (day 56).

An independent statistician will randomize the order of these two tests, and both patients and investigators blinded to the condition. A pharmacist, who will otherwise not participate in the study, will facilitate drug and placebo distribution to the subject. Unblinding information will be kept in sealed envelopes by the pharmacist in case of (S)AE. The PI will be available by beeper (24 x 7) to the subject and health care providers if unblinding would be necessary to facilitate their acute care (e.g. ER visit or hospitalization).

The endurance times at the start and completion of each treatment period (with an appropriate washout period between them) will be analyzed as the primary study outcome variable. Secondary outcome variables will be the change (fall) in inspiratory capacity at isotime during the constant work rate studies of treatment period one and two. Finally, transcutaneous $CO_2$ will be used to assess the changes in dead space to tidal volume ($V_D/V_T$) at iso-time for the two treatment periods.

***10) Visit schedule***

Written informed consent will be administered in the study center. All consenting subjects will discontinue long-acting bronchodilators (LABA and LAMA) for the entire duration of the study, and will utilize short acting beta agonists (SABA), a short acting muscarinic antagonist (SAMA), or a combination product SABA + SAMA (e.g. albuterol and ipratropium, Combivent). If the patient is on an inhaled corticosteroid in addition to his LABA (LABA+ICS), the patient will be transitioned to an inhaled corticosteroid that will be individually formulated.

The study drug (BEVESPI AEROSPHERE ® - Glycopyrrolate/Formeterol) or placebo) will be administered twice daily during two 2 week periods in the protocol. Each time, the study drug will be taken for two weeks before testing is performed with a washout between periods. The study timeline is shown in Figure 4. The study will require a total 7 visits by each patient to complete the study.

**Visit 1:** Informed Consent, Demographics, Physical Exam, BMI, Vital Signs, 12 lead EKG, Pulse Oximeter, Review of Inclusion and Exclusion Criteria, Urine Pregnancy Test (if female of childbearing age), BODE index with 6 minute walk, Spirometry, Lung Volumes/DLCO, SGRQ and CAT Questionnaires, and Chest CT with Inspiratory / Expiratory phases.

Washout of any LABA or LAMA that the patient is currently taking for 14 days. The patient will use a short acting bronchodilator (albuterol or albuterol + ipratropium). The patient will also be transitioned off of any combination inhaled corticosteroids (ICS) and onto beclomethasone or another equivalent inhaled steroid for the duration of the study.

**Visit 2**: Vital Signs, Spirometry (No Bronchodilator), Vital Signs, Ramp Pattern cardiopulmonary exercise test (CPET), followed in 2 hours with a Constant Work Rate (CWR) or "Square Wave" exercise test designed from the initial ramp pattern CPET. Both tests will have inspiratory capacity maneuvers, flow volume loop analysis and transcutaneous $CO_2$ measurements. The CWR test should be high intensity (80% of peak $VO_2$) and targeted to last between 4 and 8 minutes.

**Visit 2.5 (If Necessary)**: ** If the first CWR exercise test is not between 4 and 8 minutes in duration, a second test will be performed prior to washout. This test will be high intensity but the work rate will be adjusted from the first test by an increase or decrease of 5% (as appropriate) and targeted to last between 4 and 8 minutes. In case this test is also not within 4 and 8 minutes in duration, a third test will be performed with appropriate 5% work rate change after one hour of rest; if this test is not within 4-8 minutes in duration the patient will be considered a screen fail.

**Visit 3:** The patient will be randomized on visit 3 and have vital signs, weight, pulse oximetry, spirometry (no bronchodilator), SGRQ and CAT questionnaires. The patient will

begin treatment period # 1 of 14 days duration (either placebo or drug, randomized with respect to sequence of administration). Spirometery will be performed 30-45 minutes after administration of medication.

**Visit 4**: At the end of treatment period #1 (14 days), the subject will have vital signs, weight, and pulse oximetry, spirometry (no bronchodilator), SGRQ and CAT questionnaires and CWR exercise test with inspiratory capacity, flow-volume loop, and transcutaneous $CO_2$ measurements. The subject will administer the final dose of medication (placebo or medication) in the laboratory 45 minutes before spirometry and constant work rate testing. At this visit the patient will have the study medications stopped for another 14 day washout.

**Visit #5**: At the end of the washout from treatment period # 1, the subject will have vital signs, weight, and pulse oximetry, spirometry (no bronchodilator), SGRQ and CAT questionnaires and CWR exercise test with inspiratory capacity, flow-volume loop, and transcutaneous $CO_2$ measurements. Spirometery will be performed 30-45 minutes after administration of the new medication during the visit.

[The patient will receive the new study medications for a 14 day treatment period (treatment period # 2) of either placebo or drug; the subject will receive the alternate study drug (active medication or placebo) from what the subject received during treatment period # 1. The order will be randomized.]

**Visit # 6**: At the end of treatment period #2 (14 days), the subject will have vital signs, weight, and pulse oximetry, spirometry (no bronchodilator), SGRQ and CAT questionnaires and CWR exercise test with inspiratory capacity, flow-volume loop, and transcutaneous $CO_2$ measurements. The subject will administer the final dose of medication in the laboratory 45 minutes before spirometry and the CWR testing. At this visit the patient will have all study medications stopped and the subject will return to his/her normally prescribed medications.

**Visit # 7**: Exit and Safety Visit; vital signs, weight and pulse oximeter. Assess for adverse events and record.

## *11) Medications*

Subjects will take their daily dose of the study medication in the laboratory 90 minutes before undergoing spirometry and constant work rate testing.

### ***BEVESPI AEROSPHERE*** ® **(Glycopyrrolate/Formeterol):**

BEVESPI AEROSPHERE ® (Glycopyrrolate (GLY)/ Formeterol (FOR)) is an FDA approved (April 2016) twice daily fixed dose combination bronchodilator for maintenance

treatment of patient with COPD. The Glycopyrrolate/Formeterol is delivered by pressurized metered dose inhaler; two inhalations result in 18 micrograms of glycopyrrolate and 9.6 micrograms (µg) of formoterol. These drugs in this combination and delivery device have been studied in two randomized, double-blind, placebo-controlled, parallel group, 24 week, phase 3 studies in which patient with moderate to very severe COPD were randomized to treatment with twice daily Gly/For (19/9/6 µg), GLY (18 µg), FOR (9.6 µg), or placebo (Rabe, 2015). The primary endpoint of these studies was the change from baseline in trough $FEV_1$ at 24 weeks. A total of 3699 patients were randomized in the two studies.

*Lung Function* Treatment with GLY/FOR (18/9.6 µg) resulted in significant improvement in trough $FEV_1$ at 24 weeks compared with mono-components and placebo (Figure 5).

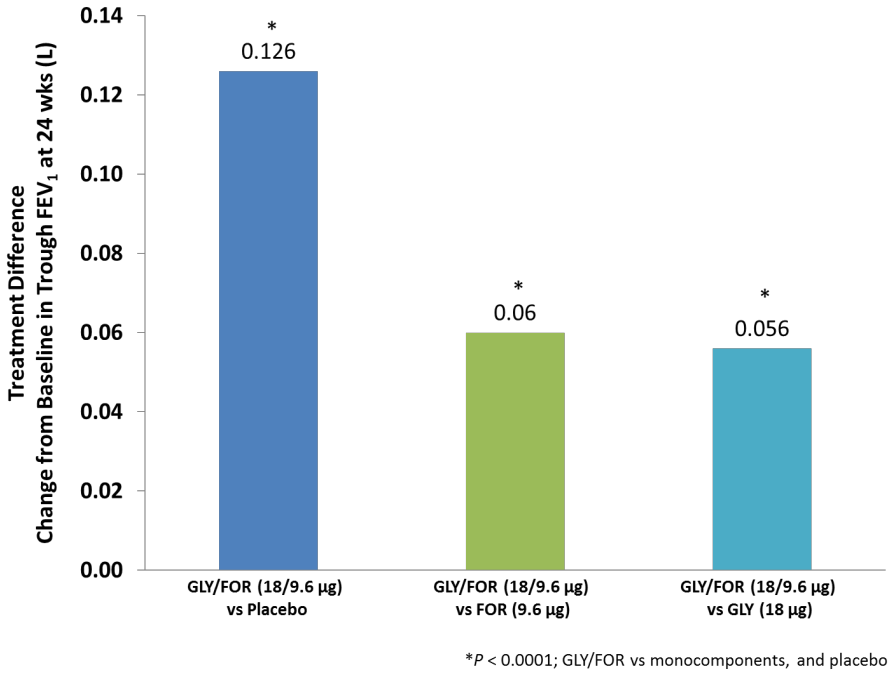


**Figure 5**: Twice Daily Glycopyrrolate/Formoterol (18/9.6 µg) FDC: Lung Function (PINNACLE-1 and PINNACLE-2, Pooled Analysis). Change in $FEV_1$ Trough at 24 weeks for GLY/For vs Placebo, GLY/FOR vs FOR, and GLY/FOR vs GLY. The change in trough $FEV_1$ is roughly double for the combination of GLY/FOR relative to either FOR or GLY alone relative to placebo.

**HRQL and Rescue Medication:** Treatment with twice daily GLY/FOR (18/9.6 µg) FDC was associated with improvement in St. George's Respiratory Questionnaire (SGRQ) total score at 24 weeks and rescue medication use compared with placebo and GLY (18 µg) monotherapy, but not with FOR (9.6 µg) monotherapy (Table 2).

**Table 2:** Glycopyrrolate/Formoterol FDC: Pooled Analysis PINNACLE-1 and PINNACLE-2

| Endpoint | GLY/FOR (18/9.6 µg) vs Placebo | GLY/FOR (18/9.6 µg) vs FOR (9.6 µg) | GLY/FOR (18/9.6 µg) vs GLY (18 µg) |
|---|---|---|---|
| SGRQ Total Score (treatment difference, change from baseline at 24 weeks) | -2.13<br>*P* = 0.005 | -0.64<br>*P* = 0.283 | -1.56<br>*P* = 0.009 |
| Daily Rescue Medication (treatment difference, puffs/day over 24 weeks) | -1.06 puffs/day<br>*P* < 0.0001 | -0.15 puffs/day<br>*P* = 0.124 | -0.42 puffs/day<br>*P* < 0.0001 |

**Safety and Tolerability:** The safety profile of twice daily GLY/FOR (18/9.6 µg) FDC in the PINNACLE-1 and PINNACLE-2 studies was similar to the monocomponents, open-label TIO, and placebo, with 60% of patients in the GLY/FOR treatment group with at least one AE compared with 56%, 57%, 58%, and 63% in the GLY, FOR, placebo and TIO groups, respectively. Over a total of 52 weeks, incidence of AEs was similar across treatment groups, with nasopharyngitis and cough the most frequently reported events, ranging from 4.3% to 6.8% and 3.4% to 4.7% of patients respectively. In patients treated with twice daily GLY/FOR (18/9.6 µg), 7.8% of patients discontinued due to AEs compared with 7.2% for GLY (18 µg), 6.0% in the FOR (9.6 µg) treatment group, and 6.2% of patients who received TIO (18 µg).

**Glycopyrrolate** is a non-chiral, long-acting, inhaled anticholinergic bronchodilator initially developed for the long-term, once-daily, maintenance treatment of bronchospasm and dyspnea associated with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema. It has had FDA approval in aerosolized form since 2014.

**Formoterol** is a long-acting beta2-adrenergic agonist bronchodilator indicated for the long-term, twice-daily maintenance bronchodilator treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema. It has had FDA approval for use in COPD since 2007.

The drug product, **BEVESPI AEROSPHERE ® Therapy (Glycopyrrolate/Formeterol)** was recently approved by the FDA (April 2016). It is delivered by ta metered dose inhaler in a fixed combination of 2 puffs equaling 18 mcg of glycopyrrolate and 9.6 mcg of formoterol.

Common side effects (more common than placebo) include:

| Adverse Reaction | BEVESPI AEROSPHERE (n=1036) % | Glycopyrrolate 18 mcg BID (n=890) % | Formoterol Fumarate 9.6 mcg BID (n=890) % | Placebo (n=443) % |
|---|---|---|---|---|
| Respiratory, thoracic, and mediastinal disorders | | | | |
| Cough | 4.0 | 3.0 | 2.7 | 2.7 |
| Infections and infestation | | | | |
| Urinary tract infection | 2.6 | 1.8 | 1.5 | 2.3 |

Other adverse reactions defined as events with an incidence of >1% but less than 2% with BEVESPI AEROSPHERE but more common than with placebo included the following: arthralgia, chest pain, tooth abscess, muscle spasms, headache, oropharyngeal pain, vomiting, pain in extremity, dizziness, anxiety, dry mouth, fall, influenza, fatigue, acute sinusitis, and contusion.

**Table 3** : Common Adverse Reactions with Bevespi Aerosphere ® (Glycopyrrolate/Formoterol FDC) (>- 2%) relative to Placebo in patients with COPD: Pooled Analysis PINNACLE-1 and PINNACLE-2

The drug package insert is attached to this application.

*Placebo* BEVESPI AEROSPHERE ® Therapy (Glycopyrrolate/Formeterol): The placebo STIOLTO™ RESPIMAT® inhaler will be prepared by AstraZeneca and contains no active therapeutic agent.

*Albuterol*: Albuterol is an FDA approved medication for pulmonary function testing. It may be used in this study as a short-acting medication during the entire study, including washout periods. The drug package insert is attached to this application.

*Combivent:* Combivent contains ipratropium bromide and albuterol. Ipratropium bromide is a marketed drug approved for use in the United States. It is a bronchodilator for maintenance treatment of bronchospasm (tightening of the airways) associated with COPD, including chronic bronchitis and emphysema. It may be used in this study as a maintenance therapy during the washout periods, but not the study periods. The drug package insert is attached to this application.

*Inhaled corticosteroids (ICS):* Some COPD patients take combination therapies that contain an inhaled corticosteroid and a long-acting bronchodilator in one dose. In these cases, patients will be transitioned to inhaled corticosteroid monotherapy for the duration of the

study. The drug package insert for a typical inhaled corticosteroid is attached to this application.

***12) Procedures***

An assessment schedule for the procedures in the study is shown in Table 4.

*Pulmonary function:* Visit 1 will include spirometry with bronchodilator albuterol, lung volume by body plethysmography, and single-breath carbon monoxide diffusing capacity tests. Each will be made according to ATS/ERS guidelines, at least 10 min after 200 µg of albuterol (Millar et al., 2005). Visits 2-7 will include spirometry measurements without albuterol.

*Resting ECG:* Visit 1 will include a resting 12 lead ECG to document that the electrocardiogram has no safety concerns prior to any exercise testing as reviewed by the principal investigator.

*Medical history and questionnaires:* During visit 1 a medical history will be collected, including respiratory and heart history, smoking history, and medication history. Patients will also complete the SGRQ and the COPD Assessment Tool (CAT) to assess COPD symptoms.

| AstraZenica Bevespi Aerosphere (Glycopyrrolate/Fometerol) Exercise Study | | | | | Treatment Period # 1 | | | | Treatment Period # 2 | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Study Phase | Informed Consent & Screening | Washout | Baseline CPET Exercise Testing | Baseline and Randomization | Treatment Period # 1 | Testing | Washout | Testing | Treatment Period # 2 | Testing | Exit Visit and Safety Visit |
| Days | -28 to -21 | (14 days) | T -3 to 7 | 1 | 1-14 | 14 | (14 days) | 28 | 28-42 | 42 | 56 |
| Window | - | - | +/- 3 | - | - | - | - | | - | - | - |
| **Visit Number** | **1** | | **2** | **3** | | **4** | | **5** | | **6** | **7** |
| Informed Consent | √ | | | | | | | | | | |
| Demographics and Medical Hx | √ | | | | | | | | | | |
| Physical Exam, BMI | √ | | | | | | | | | | |
| Vital Signs & Weight & Pulse Oximetry | √ | | √ | √ | | √ | | √ | | √ | √ |
| ECG - 12 Lead | √ | | | | | | | | | | |
| Review of Inclusion and Exclusions | √ | | | | | | | | | | |
| Urine Pregnancy Test | √ | | | | | | | | | | |
| Safety Laboratories (Blood Tests) | √ | | | | | | | | | | |
| BODE Index (with 6 minute Walk at screening) | √ | | | | | | | | | | |
| Spirometry | √ | | √ | √ | | √ | | √ | | √ | |
| Body Plethysmography and DLCO | √ | | | | | | | | | | |
| SGRQ and CAT Questionnaires | √ | | | √ | | √ | | √ | | √ | |
| Chest CT with Inspiratory and Expiratory Views | √ | | | | | | | | | | |
| Randomization | | | | √ | | | | | | | |
| Washout Medications | | √ | | | | | √ | | | √ | |
| Cardio-Pulmonary Exercise Testing - Ramp | | | √ | | | | | | | | |
| Cardio-Pulmonary Exercise Testing - Constant Work Rate | | | √ | | | √ | | √ | | √ | |
| Inspiratory Capacity and FV Loops During Exercise | | | | | | √ | | √ | | √ | |
| Transcutaneous CO2 Measurement | | | √ | √ | | √ | | √ | | √ | |
| Record Adverse Events | | | √ | √ | | √ | | √ | | √ | √ |
| Pharmacy Costs for Dispensing and Collecting Medications | | | | √ | | √ | | √ | | √ | |

**Table 4.** Assessment Schedule for the Study (see attached full page version)

*Incremental exercise test:* All patients will perform one ramp-incremental cycle exercise on an electromagnetically-braked cycle ergometer (Excalibur Sport PFM, Lode NL) to the limit of tolerance after an overnight washout of short-acting bronchodilator and a two-week

washout of long-acting bronchodilators (visit 2). Patients will breathe through a mouthpiece with nose clip in place for measurement of respired gases and volumes for breath-by-breath gas exchange and ventilatory measurements (Vmax Spectra, CareFusion USA). Tests will be administered with 3 minutes of rest and at least 3 minutes of unloaded cycling (until a steady-state is achieved), followed by an increase in power output at 5 W/min (for patients with $FEV_1 \leq 1$ L) or 8 – 20 W/min (for patients with $FEV_1 > 1$ L) and continued to the limit of tolerance. The limit of tolerance will be determined as the point at which the patient experiences intolerable dyspnea or is unable to maintain pedaling rate above 50 rpm despite verbal encouragement. At specified times during the exercise test, inspiratory capacity (IC) measurements will be made using a maximum inhalation. These will be made at rest, every 2 min during exercise, and at end-exercise.

*Constant work rate (CWR) exercise tests:* From an unloaded pedaling baseline (~3 min), the power output will be abruptly increased to approximately 80% WRpeak (this is the peak work rate achieved during the incremental exercise test). The specific work rate chosen will be chosen to elicit intolerance between 4 and 8 minutes after the first washout period (van der Vaart et al., 2014). Patients will breathe through a mouthpiece with nose clip in place for measurement of respired gases and volumes for breath-by-breath gas exchange and ventilatory measurements (Vmax Spectra, CareFusion USA). A familiarization CWR test will be performed at visit 2, at least 1 hour after the incremental test. At specified times during the exercise test, inspiratory capacity (IC) measurements will be made using a maximum inhalation. These will be made at rest, every 2 min during exercise, and at end-exercise.

The constant power test will be performed on at least 4 occasions. The initial constant power test will be made at least 2 hours after the incremental test and will be used to identify the ~6 min endurance time in untreated conditions (visit 2). If the endurance time is not in the range 4-8 minutes, then an additional visit (visit 2.5) (with the potential for one more after this, if necessary) will be made to identify required power output. After this, constant power tests will be performed to intolerance with either BEVESPI AEROSPHERE ® Therapy (Glycopyrrolate/Formeterol) or placebo (visits 4, 5, 6 and 7). The condition (active drug vs placebo) of visits 4-7 will remain blinded to the participants and the experimenters until the end of the study.

### *13) Measurements*

*Ramp Pattern CardioPulmonary Exercise Testing (CPET):* Ventilation, gas exchange, heart rate, and perceived exertion during exercise will be recorded during incremental and CWR exercise. Patients will breathe through a mouthpiece for breath-by-breath pulmonary gas exchange and ventilation measurement (Vmax Encore, CareFusion USA). Heart rate, arterial oxygen saturation, and transcutaneous $CO_2$ partial pressure will be measured. Patients will be asked to rate their perceived exertion ("rate your leg fatigue" and "rate your difficulty of breathing") every 2 minutes during exercise and recovery. All methods are well established in our laboratory.

From these measurements the following variables will be determined in the incremental test: Peak oxygen uptake, lactate threshold (LT), ventilatory equivalent for $CO_2$ at LT (as an index of ventilatory efficiency), peak ventilation (also expressed relative to maximum voluntary ventilation calculated from pulmonary function tests).

*Constant work rate testing:* From the results of the Ramp pattern CPET, a constant work rate test will be designed to last between 4 and eight minutes at baseline. This work rate will not change throughout the study, and endurance time in seconds will be recorded for each test.

*Dynamic hyperinflation (DH):* DH will be evaluated from inspiratory capacity (IC) measurements at rest, every 2 min during exercise, and at end-exercise. (Somfay et al., 2001). This reproducible method allows dynamic changes in the operational lung volume to be determined.

*Transcutaneous $CO_2$ Measurements ($tcPCO_2$):* $tcPCO_2$ and oxygen saturation (Radiometer Transcutaneous $CO_2$ Monitor (TOSCA 500) will be recorded on a breath-by-breath basis at rest and during exercise.

*Breath by Breath Flow Volume Loop Analysis (FVA*): Airflow will be recorded every 100 msec throughout the exercise tests using a digitized signal. This will be analyzed for breath-by-breath configuration of the expired flow-volume loop using special software off line.

The entire laboratory will focus on subject safety throughout the study. This includes investigator involvement with all screening, medical history, physical examinations, laboratories, EKG, PFTs, and CPET results. This also includes real time assessment of all physiologic variables (heart rate, blood pressure, oxygen uptake, carbon dioxide output, ventilation, oxygen saturation, transcutaneous $CO_2$, and EKG tracings at all times during exercise testing.

## a) Data and Specimen Banking*

N/A

## b) Data Management *

### 1) Training on Data Management

a. All individuals involved with the project, including data analysis and management will complete the LA BioMed training requirement regarding human research, data security and protection of personal information (Collaborative Institutional Training Initiative (CITI)).

**2) Electronic Data**

Referencing the Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center (LA BioMed) Computer Security and Privacy Policy (from Dr. Kevin Dawson, Vice President of Information Services at LA BioMed):

LA BioMed has implemented a comprehensive security/privacy framework to safeguard protected health information, personally identifiable data, and other confidential or classified data on storage media, in computers, and in transit. LABIOMED and the CDCRC have administrative, physical, and technical safeguards enforced and in place.

a) **Administrative Safeguards:**

- An Information Security Policy has been published and is enforced. It controls access to information resources, anti-malware management, vulnerability testing, password rules, privileged access, network infrastructure management, encryption of laptops and portable devices, compliant hardware, software, and services, and the annual review of the policy. An Accessible Use Policy of Computer Equipment is included in the Employee Handbook.
- All LA BioMed employees are hired after passing a background investigation. Employees working with electronic data need to take HIPAA training and pass a test. An Employee Onboarding, Transfer, and Offboarding Policy controls granting and revoking access to information resources when employment status is changing.

b) **Physical Safeguards:**

- Our data center is protected by a key card entry system. The building itself is also protected by a key card entry system. Key cards are assigned to authorized personnel only and an entry log is maintained for future audits. Switch cabinets are protected by combination locks and/or metal keys. Key wiring closets and IS storage areas are protected by individual numeric keypad locks. Entry codes are assigned on an individual basis. Entry logs can be downloaded from the locks onto a computer for future audits.

c) **Technical Safeguards:**

- Access to all computers containing business data are password protected. A strong password policy and 90 days renewal policy is enforced. Access to our wireless network is encrypted and password protected. Remote access to computer resources is granted through Secure Socket Layer-encrypted Virtual Private Network (SSL VPN). Access to individual enterprise applications are also password-protected. Access to individual computers, SSL VPN, emails, wireless network, and most enterprise applications is managed through Active Directory (AD) single sign-on. This gives us the ability to revoke all access if necessary by a single action.

All computers attached to our network must comply with minimal acceptable security safeguards. This includes a malware detection software be installed, running, and regularly updated and an updated and patched operating system. The policy is enforced by a network scanning application. Our network is protected by hardware firewall and intrusion prevention and detection systems (IPS/IDS). Hardware decommissioning includes the step of physically destroying or wiping all storage media with a Department of Defense (DoD)-compliant wipe application.

**3) Physical and Identifiable / Confidential Data**

Physical Data will be stored in secure, locked filing cabinets in the LABIOMED CDCRC Building. In order to minimize the risk of inappropriate use of medical information, no data will be labeled in a way that they can be readily identified to an individual. Participants' data will de-identified using a number code system and the key will be kept in a locked cabinet in the PI's office or records room. Access to identifiable data will be limited to members of the study team (PI and Study Coordinators). No protected health information (PHI) will be transmitted via email or on portable devices.

**4) Data Analysis Plan for the Study**

***Power calculation***

In making the sample size calculation, we have selected a two-sided test.

We will also assert that the study should powered to at least 80%.

The two remaining variables necessary for the sample size calculation are the posited test duration effect size associated with the intervention and the posited standard deviation of the change in test duration among subjects associated with the intervention. We deal with these separately:

- Standard deviation of change. This has been estimated in placebo-controlled COPD studies in which the standard deviation of constant work rate (CWR) exercise duration has been assessed between tests done at baseline and post-placebo administration. Values in the range of 180 seconds were seen (Casaburi, 2005). A more recent study tended to confirm this. In a study of 111 COPD patients, the change in CWR duration in response to placebo had a standard error of 17 seconds (SD of 179 seconds) (Casaburi et al., 2014). However, a key determinant of the magnitude of change of CWR duration is the baseline test duration (longer baseline duration predicts larger change in CWR duration for a given intervention). Previous studies generally did not carefully control baseline CWR duration between 4 and 8 minutes (as we propose here,

and as proposed in a recent ERS guideline (Puente-Maestu et al., 2016)). Baseline durations outside this range predictably increase the SD of the change in duration following intervention. Furthermore, these studies were generally multicenter trials, which can be argued to add to variability, in itself. We therefore feel that an estimate of 180 seconds is conservative.

- Effect size. This can be chosen considering 1) changes in CWR duration considered clinically significant (MCID) and 2) improvements in CWR duration seen in other combination bronchodilator trials or extrapolation of improvements seen in single bronchodilator trials.

  - As to the MCID, the best figure available is approximately 105 seconds (Puente-Maestu et al., 2016). From the most recent ERS statement: "In COPD, 100-s (95% CI 60–140 s) or 33% (95% CI 18–48%) change from baseline using cycle ergometry related well with positive patient-reported outcomes after pulmonary rehabilitation."

  - As to the effect size to be expected from dual bronchodilator therapy, 4 studies are included in the recent ERS statement referred to above. Increases in CWR duration average 60, 95, 410 and 310 seconds. The same analysis shows that single bronchodilators are associated with increases (though variable) averaging about 90 seconds. A recent report of umeclidinium + vilanterol showed a ~50 second improvement vs. placebo ((Maltais et al., 2014)) and a poster at ATS in 2015 showed a 68 second increase with tiotropium + olodaterol vs placebo (O'Donnell et al.)

We have chosen 60 seconds for an effect size; this corresponds to the lowest range of observed effect sizes and is well below the MCID. This choice can be seen to be highly conservative.

**Table 5.** Sample size for a range of effect size and standard deviation of change in CWR duration for combination bronchodilator therapy

| | | **Effect size** | | |
|---|---|---|---|---|
| | | **60 s** | **80 s** | **90 s** |
| **SD of change in duration** | **100 s** | 24 | 15 | 12 |
| | **120 s** | 34 | 20 | 16 |
| | **150 s** | 52 | 30 | 24 |
| | **180 s** | 73 | 42 | 34 |

As can be seen, the suggested sample size of 40 will be inadequate only if *both* the most conservative estimates of effect size and standard deviation are chosen (in red). **We therefore propose 50 subjects as a good balance between these issues.**

**Analysis Plan**

It is hypothesized that BEVESPI AEROSPHERE ® (Glycopyrrolate/Formeterol) will improve exercise endurance time relative to placebo. We also believe this medication combination relative to placebo will reduce dynamic hyperinflation as measured by inspiratory capacity, VD/VT measurements from the non-invasive transcutaneous CO2 measurements, and show less evidence of coving in the expiratory limb of the flow-volume loops during exercise.

Differences in endurance time (seconds) between BEVESPI AEROSPHERE ®(Glycopyrrolate/Formeterol) and placebo on the constant work rate high intensity test will be assessed using a mixed model with covariate adjustment for baseline endurance time and period and by treating subject as a random effect to account for within subject correlation. Statistical significance will be declared if two-sided p is less than or equal to 0.05.

We will analyze the difference in isotimes between BEVESPI AEROSPHERE® (Glycopyrrolate/Formeterol) and placebo for inspiratory capacity, VD/VT and RAR. These will also be assessed in a similar manner to exercise endurance time.

## c) Confidentiality

Source Documents: These will include all data with patient demographics, history, questionnaires, pulmonary function, and exercise testing results. The documents will be filed in the subject's source document binder. This binder will also contain the properly executed consent form, the HIPAA (PHI) form as well as demographic data.

The patient identifiers will be kept in this folder, but under a separate section from the study source data. This section will be marked as 'confidential' and the binders will be kept in a locked cabinet in a locked room. Access to the patient identifiers will be permitted only for the study coordinator, the investigators and person(s) with direct contact with the patient.

<u>Source Documents / CF / Identifying Information / Electronic Data</u>

- Physical Data (paper based) will be stored locally in locked cabinets in the LABIOMED CDCRC building for 3 years after the study is completed.
- Only the PIs and Study Coordinators will have access to PHI. All others involved with data analysis and presentation, including AZ will have de-identified data.

- A unique ID will be created along with a log that connects the ID to the subject's PHI. The document that connects the unique ID to the subject's PHI will be kept in a locked cabinet along with the consent forms.
- The subjects name and other identifiers will be stored separately from both paper and electronic data. The identifier log will be destroyed 3 years after the study is completed.
- Electronic data will be stored on password protected personal computers in the LABIOMED CDCRC building, per LABIOMED Computer Security and Privacy Policy.
- No identifiable data will be transferred via either email or portable disk.

- Only de-identified data will be available for the sponsoring company to review, unless a compelling reason is presented to the local IRB for approval.

## d) Provisions to Monitor the Data to Ensure the Safety of Subjects*

The PI will be responsible for reporting any adverse events to the local IRB utilizing the adverse event reporting policy established by the local IRB. All serious adverse events and non-serious adverse events which are relevant for a reported serious adverse event and Adverse Events of Special Interest (AESI) shall be reported to AstraZeneca, Inc. Data monitoring will be made on a per-procedure basis by the PI or co-investigators.

Per its policy, periodic audit for study conduct in compliance with regulations, Good Clinical Practice, etc will be undertaken for this study by a member of the Compliance Office at Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center.

The assigned Astra Zeneca Medical Study Leader will maintain direct communications with the site, and will set up quarterly visits with the PI to provide AZ support by managing any study or contractual questions or concerns the site have. However, the medical study leader will not review nor perform source documentation validation of any kind.

## e) Withdrawal of Subjects*

Participants will be free to withdraw from the study at any time. Participants may choose to stop study treatment or leave the study at any time without it affecting their future care. Subjects are asked to discuss the decision to leave the study with the study

doctor. Subjects will be asked to return to the clinic for a follow-up visit and to return any unused study medication, but do not have to do this.

Participants are told that the study doctor may decide to withdraw them from this study at any time even without their consent. Participants will be withdrawn for any of the following reasons:

- Consent is withdrawn
- The subject is unwilling or unable to follow the rules of the protocol
- The subject becomes pregnant
- The subject experiences a medical emergency that makes it necessary to stop taking study treatment or that requires treatment assignment to be revealed to the study doctor and/or staff
- At the decision of the PI of one of the participating physicians

## f) Publication Policy

The investigators are dedicated to support process of free exchange of relevant scientific information. The rights of the investigators and of the sponsor with regard to publication of the results of this trial are described in the investigator contract. As a general rule, no trial results should be published prior to finalization of the Clinical Trial Report.

# 14) Risks to Subjects*

*Identification of risk and protections to minimize risk*

**Exercise**

Our primary concern is the safety of the participant during exercise testing. Participants will perform high-intensity exercise that may lead to physical discomforts (e.g. fatigue, delayed onset muscle soreness), but especially dyspnea in this patient population. The risks associated with participating in this study may include, although unlikely: muscle cramps, muscle strain and/or joint injury, delayed muscle soreness, dyspnea, syncope, and fatigue. They may feel delayed muscle soreness (24-48 hours) after exercise. There is a risk of a cardiac event, such as cardiac ischemia, cardiac arrest, dangerous arrhythmia, or acute cardiac collapse. This risk is approximately 1-2 occurrences in 10,000 tests of 'high risk' subjects with cardiovascular disease (American College of Sports Medicine). Similarly, an assessment of risk during high-intensity interval exercise testing and training of patients with coronary heart disease revealed approximately 1 event in over 23,000 hours of exercise, such as arrhythmia or myocardial infarction (Rognmo et al., 2012).

A person trained in basic cardiac life support (ACLS) CPR will be present during testing and a defibrillator is located within the laboratory in case of a cardiac event. A licensed physician will be available within the CDCRC for all exercise testing study visits and will be

in the room during each subject's initial incremental exercise test. Participants will be coached and queried during testing to identify for the investigators any unexpected symptoms and the exercise stopped immediately to mitigate risk during exercise testing. All tests are done with a 12-lead ECG and the test is stopped should arrhythmic or ischemic patterns develop. All tests are done with pulse oximetry and the exercise will be stopped should oxygen saturation fall below 85%.

**Medications**

All medications have the potential to cause side effects. The drugs involved in this study may involve risks that are already known, as well as risks that are currently unknown. Serious allergic reactions that can be life threatening may occur with any medication. However, we will take precautions to reduce these risks. Patients will be instructed to immediately report any allergic reactions to the PI, such as:

- rash
- difficulty breathing
- wheezing
- sudden dizziness, especially when standing
- swelling around the mouth, throat, or eyes
- fast pulse
- sweating

Short Acting Bronchodilator Medications

The study utilizes a crossover design. Prior to beginning each new treatment period, a 2 week washout from the study drug, usual medications, or placebo is required. This means that the COPD patients in the study will be asked not to take long-acting beta agonists (LABA) or long acting anticholinergic (LAMA) for two, 2 week periods during the study. In addition, during both of the two, 2 week treatment periods, the patient will be using a short acting bronchodilator medication (albuterol) as their rescue medication.

During the washout and placebo time windows, subjects will be provided with a short-acting brochodilator replacement medication (albuterol, or in some cases, Combivent) and be given instructions how to use it. In addition, any patients on combination therapies that include a long-acting bronchodilator will be required to discontinue its use prior to the study. This may include combination inhaled corticosteroid medications. The patient can continue on inhaled corticosteroids, as long as it is an isolated preparation (not associated with a LAMA or LABA).

The transition from longer acting medications to shorter acting medications of the same class during the two wash out periods (2 weeks each) can result in side effects, including increased dyspnea, particularly on exertion, and a need for increased rescue inhaler use. In addition, there is a risk that the subject will have an exacerbation (or COPD exacerbation) that may require additional medications, such as inhaled or oral corticosteroids, antibiotics, a doctor's office visit, an emergency room visit, or even hospitalization.

These risks are felt to be low and mitigated by the following interventions:

1) subjects will continue with their short acting medications.
2) The subject can continue inhaled corticosteroids if they were present prior to enrollment,
3) the selected enrollment criteria excludes the most severe COPD patients (must be > = 35% of their predicted FEV1),
4) the investigators will be following the patients very closely during the washout period with instructions to call if any difficulty breathing or reduced exercise tolerance.

Although the risk is low, it is certainly possible that some subjects will not tolerate changing the long acting medications to shorter acting ones of the same categories, and may have to be dis-enrolled and restarted on their usual medications. It is also possible that participation in the study could cause a doctor's office visit, emergency room visit, or potentially a hospitalization.

**Albuterol**

Four puffs of albuterol will be given at visit 1 during the lung function tests, and will be provided as a short-acting bronchodilator medication. Albuterol is an FDA approved bronchodilator with mild side effects. Reported risks include:

- Very common (greater than 10%): Pharyngitis (sore throat).
- Common (3% - 7%): Headache, rapid heart rate, muscle and joint pain, dizziness, stuffy and runny nose, and unpleasant awareness of palpitations (strong heart beat).
- Uncommon (less than 3%): Chest pain, infection, diarrhea, inflammation of the tongue, accidental injury, anxiety, shortness of breath, ear disorder, ear pain and urinary tract infection.

**Combivent**

Combivent is an FDA approved short-acting bronchodilator containing albuterol and ipratropium bromide.

- Common side effects (greater than 2%) associated with Combivent include: Cough, shortness of breath, headache, bronchitis, sore throat, respiratory infection
- Uncommon side effects (less than 2%) include: High blood pressure, dizziness, tremor, muscle spasms or muscle pain, diarrhea, nausea, dry mouth, constipation, vomiting, weakness, flu-like illness, chest discomfort, eye pain, low blood potassium, palpitations (strong heat beat), fast heartbeat, skin itching or rash, pain in nose or throat, wheezing

Patients taking an inhaled corticosteroid (combined therapy) will transition to an FDA approved monotherapy corticosteroid at the beginning of the study. Risks of corticosteroids include:

- Common side effects (greater than 3%) associated with inhaled corticosteroids include: upper respiratory infections, throat irritation, upper respiratory inflammation, sinus infection, hoarseness, mouth or throat infection, cough, bronchitis, headache
- Uncommon side effects (less than 3%) include: runny nose or post-nasal drip, nasal sinus disorders, laryngitis, diarrhea, viral gastrointestinal infections, dyspeptic symptoms,

gastrointestinal discomfort and pain, dry mouth, joint pain, muscle pain, muscle stiffness/tightness/rigidity, dizziness, migraines, fever, viral infections, pain, chest symptoms, viral skin infections, muscle injuries, soft tissue injuries, urinary infections

**Study Medications**

*Placebo BEVESPI AEROSPHERE®*
There are no known risks associated with using the placebo *BEVESPI AEROSPHERE®*

*BEVESPI AEROSPHERE®*
Combination treatment with glycopyrrolate and formeterol (*BEVESPI AEROSPHERE®* ) has been studied in 12 completed clinical trials. It is delivered by a metered dose inhaler in a fixed combination of 2 puffs equaling 18 mcg of glycopyrrolate and 9.6 mcg of formoterol.

The two studies for Bevespi Aerosphere® included 4,911 subjects with COPD in two 24 week lung function trials, one long term safety extension study of 28 weeks, and 10 other trials of shorter duration. A total of 1,302 subjects have received at least one dose of Bevespi Aerosphere ®. The safety data described below is based upon the two 24 week trials and the one 28 week long term safety extension trial. Adverse reactions observed in the other trials were similar to those observed in these confirmatory trials.

Common side effects (> 2 % and more common than placebo) in COPD patients relative to placebo include:

| Adverse Reaction | BEVESPI AEROSPHERE (n=1036) % | Glycopyrrolate 18 mcg BID (n=890) % | Formoterol Fumarate 9.6 mcg BID (n=890) % | Placebo (n=443) % |
|---|---|---|---|---|
| Respiratory, thoracic, and mediastinal disorders | | | | |
| Cough | 4.0 | 3.0 | 2.7 | 2.7 |
| Infections and infestation | | | | |
| Urinary tract infection | 2.6 | 1.8 | 1.5 | 2.3 |

Other adverse reactions defined as events with an incidence of >1% but less than 2% with BEVESPI AEROSPHERE but more common than with placebo included the following: arthralgia, chest pain, tooth abscess, muscle spasms, headache, oropharyngeal pain, vomiting, pain in extremity, dizziness, anxiety, dry mouth, fall, influenza, fatigue, acute sinusitis, and contusion.

The drug package insert is attached to this application.

Specifically:
The following side effects occurred in more than 3% of subjects:

- cough (4.0% vs 2.7%)
- urinary tract infection (2.6% vs 2.3% placebo)

Other side effects that occurred in > 1%, but less than 2% of patients are:

- arthralgia
- chest pain
- tooth abscess
- muscle spasms
- headache
- oropharyngeal pain
- vomiting
- pain in extremity
- dizziness
- anxiety
- dry mouth
- fall
- influenza
- fatigue
- acute sinusitis
- contusion

Pulmonary Function Testing

Pulmonary function tests represent minimal risk and are done routinely. In the past fifteen years there has been no adverse event precipitated by pulmonary function tests in our laboratory. Some people find the breathing tests tiring and occasionally patients experience a sense of dizziness, headache or shortness of breath that usually resolves quickly (common, mild seriousness). A few may experience a feeling of claustrophobia while in the body plethysmograph. This usually passes as soon as the door is opened (uncommon, mild seriousness). The carbon monoxide content of the gas mixture used to measure lung diffusion capacity is low (0.3%) and the duplicate tests are done five minutes apart; therefore this test does not significantly increase blood carboxy-hemoglobin concentration.

Questionairres

The risks associated with reading and filling out questionnaires are, rarely, some psychological discomfort and anxiety.

Chest CAT Scans

The risks associated with the Chest CAT scans are related to ionizing radiation. For this study, the subjects will be exposed to radiation during the two chest CT scans (inspiratory and expiratory). The maximum amount of radiation exposure during these 2 chest CT scans is about 900 millirads (mrads). A millirad is a measurement of radiation. The average amount of background radiation (present in our daily environment) that most people are exposed to in the United States is about 300 mrads per year. That means that the radiation

received during this chest CT scan is equal to the amount received through our normal environment on a daily basis spread over a 3 year period. For the sake of comparison, other estimated doses of medical radiation are: chest x-ray (25 mrads), set of dental x-rays (750 mrads) and barium enema x-ray (2000 mrads). The more radiation received over the course of a person's life, the greater the risk of developing cancerous tumors or of causing changes in the genes. Women who are pregnant will not be given a chest CT scan because of possible risks to an unborn child.

Personal Information Risk

Only personal information essential to the research will be recorded, including age, anthropometric data such as height and weight, and physiologic data gathered during the experiments. These variables are important to describe the patients enrolled for future publications. Personal health information is protected by conducting all data collection, storage, or transfer according to HIPAA Privacy regulations. None of the data are considered to be sensitive or place the subject at legal risk. Personally identifiable data will not be disclosed to anyone other than the research team without the written consent of the subjects or their legal representative. PHI linking the data to the subject will be destroyed 3 years after study completion.

## 15) Potential Benefits to Subjects*

There are no direct benefits to the subjects from their participation in the study.

## 16) Provisions to Protect the Privacy Interests of Subjects

The collection of data will be within the confines of the LABIOMED CDCRC building. The CDCRC Building has private offices and examination rooms that ensure subject privacy away from other ongoing activities and personnel. Only investigators and the necessary support staff will interact with the subjects during historical and experimental data collection.

The investigators and the support personnel involved are highly experienced with appropriate interaction with research subjects. This expertise and the physical means of providing privacy (see above) are the main methods in place in order to maximize the subjects' sense of ease during the study-related activities.

The patients' historical and experimental data will be secured. Only the investigators and the necessary support personnel with a need to know will have access to the files.

Subjects are informed in the consent form:

"We will do our best to make sure that the personal information in your medical record is kept private. However, we cannot guarantee total privacy. We may have to give out your personal information if required by law. If information from this study is published or presented at

scientific meetings, we will not use your name or other personal information that can identify you.

Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- The maker of the study medication, AstraZeneca Inc., and its representatives
- The Office of Human Research Protection and other government agencies, like the Food and Drug Administration (FDA), involved in keeping research safe for people
- The Institutional Review Board at the Los Angeles Biomedical Research Institute or its staff

The ways your study doctor will use your study-related health information and the people who may receive it are identified in a separate form entitled Authorization For Release of Protected Health Information (PHI)."

## 17) Compensation for Research-Related Injury

Participants are informed:

"If you are injured because of your taking part in this research study medical care will be available. This care will not necessarily be free of charge. If you are injured as a direct result of taking the drugs used in this study or as a result of a procedure that would not have been performed on you if you were not in the study, you will be provided with appropriate medical care including treatment and hospitalization if necessary. The care will not necessarily be free of charge. Financial compensation for any injury from this research is not available. The study sponsor Los Angeles Biomedical Research Institute will not pay for the normal progress of your disease, or any injury or complication due to the medical condition you already have. Financial compensation for such things as lost wages, disability or discomfort due to an injury is not available."

## 18) Economic Burden to Subjects

Participants are informed:
"You do not have to pay for study drugs, study visits, supplemental medications or tests that are part of the study.

The study drug/placebo, supplemental (rescue) medications and all tests and procedures required for this study at no cost and will be paid for by the study grant.

## 19) Consent Process

Informed consent will be obtained at the CDCRC Building in a private office before any study-related procedures are performed. Subjects will be told that they have as much time as they need to consider the consent information, and will be given the opportunity to discuss the study with friends, family and their health care provider. At each visit, subjects will be reminded that participation in the study is voluntary and their questions, if any, will be answered. We will follow the SOP: Informed Consent Process for Research (HRP-090).

***Non-English Speaking Subjects***
Since our area has a significant Spanish-speaking population, this ethno-linguistic population will also be considered for recruitment. An IRB-approved Spanish Language Consent form will be officially produced if needed. Several of the study associates are natively fluent in Spanish and will assist with communication during the actual experiments.

***Waiver or Alteration of the Consent Process (consent will not be obtained, required information will not be disclosed, or the research involves deception)***
Not Applicable.

***Subjects who are not yet adults (infants, children, teenagers)***
Subjects who are not yet adults are excluded from this research.

***Cognitively Impaired Adults***
Subjects who are cognitively impaired are excluded from this research.

***Adults Unable to Consent***
Adults who are unable to consent are excluded from this research.

## 20) Process to Document Consent in Writing

We will follow the standard operating procedure (Written Documentation of Consent; HRP-091) for written documentation of consent.

## 21) Vulnerable Populations

Vulnerable populations such as, pregnant women, adults unable to give consent, individuals who are not yet adults and prisoners are excluded from this research.

## 22) Drugs or Devices

The study drug, *BEVESPI AEROSPHERE ®* (Glycopyrrolate/Formeterol) and matching placebo, will be prepared by the manufacturer who is experienced in placebo

controlled trials. Medication will be packaged with a coded label and shipped to each study site. The LA BioMed Research Pharmacy will prepare blinded study medication, utilizing randomization codes supplied by an independent statistician who is otherwise not involved in the study. Blinded drug supply for each patient will be kept in temperature and humidity controlled cabinets in the Research Pharmacy.

The study drug and matching placebo will be provided by AstraZeneca Inc. Supplemental medication (albuterol, Combivent, and ICS) will be obtained commercially by the research team. These drugs will be stored in a locked cabinet in the Drug Supply Room in the CDCRC and supplied to study participants as needed in unblinded containers.

## 23) Multi-Site Human Research*

Not applicable.

## 24) Community-Based Participatory Research

Not applicable.

## 25) Sharing of Results with Subjects

The results of this study will not be shared directly with the participants. As part of the consent process it will be explained to the participants that they can contact the Principal Investigator should they wish to find out about the results of the study, or for any other information about the study.

The results of the pulmonary function tests, CT scans, and cardiopulmonary exercise tests may be shared with the patient on request. Patients are likely to have performed these tests previously, and the results of this test may provide information on the progression of their disease. Patients will be provided with a copy of their incremental exercise test results on request. Information on pulmonary function or clinical exercise testing will be provided by the PI or participating physician. Other results will be explained on request by the PI or his staff, but these are experimental procedures and have no specific diagnostic or clinical benefit to the individual patient.

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