

TRIPLE COMBINATION THERAPY FOR COPD**CROSS-REFERENCE TO RELATED APPLICATION**

This application claims the benefit of priority to U.S. Provisional Application No. 63/557,446; filed February 23, 2024, the content of which is hereby incorporated by reference in its entirety for all purposes.

FIELD

[001] The present disclosure provides a method of treating chronic obstructive pulmonary disease (COPD) in a subject, comprising administering to the subject twice daily a therapeutically effective dose comprising a composition comprising budesonide, glycopyrronium and formoterol fumarate, wherein the dose is administered to the subject via a metered dose inhaler, wherein the subject is at an elevated risk of a COPD exacerbation event and cardiovascular disease.

BACKGROUND

[002] Globally, chronic obstructive pulmonary disease (COPD) and cardiovascular disease are leading causes of death with overlapping pathophysiological drivers. COPD increases the risk of cardiovascular events, with cardiovascular disease being the most common cause of death in people living with COPD.

[003] Inhaled triple combination therapies containing an inhaled corticosteroid (ICS), long-acting muscarinic antagonist, and long-acting β_2 -agonist have been shown to reduce COPD exacerbation rates and improve lung function compared with dual therapies without ICS. Data from previous studies support a benefit of triple therapy with budesonide/glycopyrrolate/formoterol fumarate (BGF) versus dual therapy with glycopyrrolate/formoterol fumarate (GFF) on all-cause mortality in patients with COPD (Rabe et al. *N Engl J Med* 2020;383(1):35-48). Despite people with severe cardiac disease (e.g., congestive heart failure [New York Heart Association Class III/IV], clinical significant abnormal electrocardiogram, clinically uncontrolled hypertension) being excluded from ETHOS, cardiovascular-related deaths were the most common cause of death in the study and major adverse cardiac events were lower with

BGF versus GFF (Martinez et al. *Am J Respir Crit Care Med* 2021;203(5):553-564; Bafadhel et al. *Eur Respir J* 2021;58: RCT208).

SUMMARY

[004] In some embodiments, the present disclosure provides a method of treating chronic obstructive pulmonary disease (COPD) in a subject, comprising administering to the subject twice daily a therapeutically effective dose comprising a composition comprising budesonide, glycopyrronium and formoterol fumarate, wherein the dose is administered to the subject via a metered dose inhaler, wherein the subject is at an elevated risk of a COPD exacerbation event and cardiovascular disease. In some embodiments, the present disclosure provides a use of a composition comprising budesonide, glycopyrronium, and formoterol fumarate in the manufacture of a medicament for the treatment of chronic obstructive pulmonary disease (COPD) in a subject, wherein the subject is at an elevated risk of a COPD exacerbation event and cardiovascular disease, and wherein the medicament is administered twice daily with a therapeutically effective dose via a metered dose inhaler.

[005] In some embodiments, the method or use (i) reduces risk of a severe COPD exacerbation event by at least about 10%, (ii) reduces risk of a severe cardiac event by at least about 10%, or (iii) reduces risk of a severe COPD exacerbation event by at least about 10% and reduces risk of a severe cardiac event by at least about 10% as compared to administration of a composition comprising a same dose of glycopyrronium and formoterol fumarate but no budesonide.

[006] In some embodiments, the method or use reduces risk of a severe COPD exacerbation event by at least about 15%, at least about 20%, at least about 30% or at least about 40% as compared to administration of a dose comprising a composition comprising glycopyrronium and formoterol fumarate but no budesonide.

[007] In some embodiments, the method or use reduces risk of a severe cardiac event by at least about 15%, at least about 20%, at least about 30% or at least about 40% as compared to administration of a dose comprising a composition comprising glycopyrronium and formoterol fumarate but no budesonide.

[008] In some embodiments, the subject's forced expiratory volume in 1 second area under the curve from 0-6 hours (FEV₁ AUC₀₋₆) at 12 weeks following administration of the composition is greater than 110 mL

[009] In some embodiments, the subject's FEV₁ AUC₀₋₆ at 12 weeks following administration of the composition is at least 10% higher as compared to administration of a dose comprising a composition comprising glycopyrronium and formoterol fumarate but no budesonide.

[010] In some embodiments, the subject's trough FEV₁ at 12 weeks following administration of the composition is greater than 90 mL.

[011] In some embodiments, the subject's trough FEV₁ at 12 weeks following administration of the composition is at least 10% higher as compared to administration of a dose comprising a composition comprising glycopyrronium and formoterol fumarate but no budesonide.

[012] In some embodiments, the dose administered comprises about 220 to about 420 µg, about 270 to about 370 µg, about 300 to about 340 µg, or about 320 µg budesonide.

[013] In some embodiments, the dose administered comprises about 5 to about 35 µg, about 10 to about 25 µg, about 15 to about 20 µg, or about 18 µg glycopyrronium.

[014] In some embodiments, the dose administered comprises about 2 to about 20 µg, about 5 to about 15 µg, about 8 to about 12 µg, or about 10 µg formoterol fumarate.

[015] In some embodiments, the dose administered comprises about 300 to about 340 µg budesonide, about 15 to about 20 µg glycopyrronium, and about 8 to about 12 µg formoterol fumarate. In some embodiments, the dose administered comprises about 320 µg budesonide, about 18 µg glycopyrronium, and about 9 µg to about 10 µg formoterol fumarate.

[016] In some embodiments, the dose comprises delivering two metered doses from the metered dose inhaler. In some embodiments, each metered dose of the two metered doses comprises about 100 to 200 µg budesonide. In some embodiments, each metered dose of the two metered doses comprises about 2 to 20 µg glycopyrronium. In some embodiments, each metered dose of the two metered doses comprises about 1 to 10 µg formoterol fumarate. In some embodiments, each metered dose of the two metered doses comprises about 140 to 180 µg

budesonide, about 5 to about 15 µg glycopyrronium and about 3 to about 8 µg formoterol fumarate. In some embodiments, each metered dose of the two metered doses comprises about 160 µg budesonide, about 9 µg glycopyrronium and about 5 µg formoterol fumarate.

[017] In some embodiments, the composition comprises budesonide and glycopyrronium at a ratio of about 15:1 to about 20:1 (wt/wt) or about 16:1 to about 19:1 (wt/wt).

[018] In some embodiments, the composition comprises budesonide and formoterol at a ratio of about 30:1 to about 40:1 (wt/wt) or about 32:1 to about 35:1 (wt/wt)

[019] In some embodiments, the budesonide, glycopyrronium and formoterol fumarate are in the form of particles, wherein at least 90% of the particles by volume comprise an optical diameter of about 1 µm to about 7 µm.

[020] In some embodiments, the method or use provides a hazard ratio less than about 0.9 or less than about 0.7 for severe COPD exacerbation events as compared to administration of a composition comprising a same dose of glycopyrronium and formoterol fumarate without budesonide. In some embodiments, the method provides a hazard ratio less than about 0.9 or less than about 0.7 for severe cardiac events as compared to administration of a composition comprising a same dose of glycopyrronium and formoterol fumarate without budesonide.

[021] In some embodiments, the method or use provides an annualized severe COPD exacerbation event rate at least about 15% or at least about 25% lower as compared to administration of a composition comprising a same dose of glycopyrronium and formoterol fumarate without budesonide. In some embodiments, the method provides an annualized severe cardiac event rate at least about 15% or at least about 25% lower as compared to administration of a composition comprising a same dose of glycopyrronium and formoterol fumarate without budesonide.

[022] In some embodiments, the composition comprises micronized particles of budesonide. In some embodiments, the composition comprises micronized particles of glycopyrronium. In some embodiments, the composition comprises micronized particles of formoterol fumarate. In some embodiments, the composition comprises a plurality of budesonide particles, a plurality of glycopyrronium particles, a plurality of formoterol fumarate particles, a plurality of respirable

suspending particles, and a suspension medium, wherein the plurality of budesonide particles, the plurality of glycopyrronium particles, the plurality of formoterol fumarate particles and the plurality of suspending particles are co-suspended in the suspension medium to form a co-suspension.

[023] In some embodiments, the suspension medium is a pharmaceutically acceptable propellant selected from a hydrofluoroalkane (HFA) propellant, a hydrofluoroolefins (HFO) propellant, a hydrofluorocarbon propellant (HFC), and combination thereof. In some embodiments, the suspension medium is a propellant of pharmaceutical grade (1E)-1,3,3,3-Tetrafluoro-1-propene (HFO-1234ze(E)).

[024] In some embodiments, the respirable suspending particles comprise a volume median optical diameter of about 0.2 μm to about 50 μm . In some embodiments, the respirable suspending particles are about 1 mg/mL to about 30 mg/mL in the suspension medium.

[025] In some embodiments, the respirable suspending particles comprise a phospholipid. In some embodiments, the phospholipid is 1,2-Distearoyl-sn-glycero-3-phosphocholine (DSPC).

[026] In some embodiments, a weight ratio of total mass of the respirable suspending particles to total mass of the budesonide, glycopyrronium and formoterol fumarate particles is about 1.5:1 to about 200:1.

[027] In some embodiments, the subject is not administered greater than 8 metered doses in a 24 hour period.

[028] In some embodiments, the present disclosure provides a method for decreasing the mortality of a subject suffering from COPD and a cardiovascular disease, the method comprising administering to the subject twice daily a therapeutically effective dose comprising a composition comprising budesonide, glycopyrronium and formoterol fumarate, wherein the dose is administered to the subject via a metered dose inhaler. In some embodiments, the present disclosure provides a use of a composition comprising budesonide, glycopyrronium, and formoterol fumarate in the manufacture of a medicament for decreasing the mortality of a subject suffering from chronic obstructive pulmonary disease (COPD) and a cardiovascular disease, wherein the medicament is administered twice daily with a therapeutically effective dose via a

metered dose inhaler. In some embodiments, the mortality is all-cause mortality. In some embodiments, the all-cause mortality of the subject is reduced by at least about 20%, at least about 30%, or at least about 40% compared to a method or use comprising administering a composition comprising glycopyrronium and formoterol fumarate without budesonide. In some embodiments, the all-cause mortality of the subject is reduced by at least about 10% compared to a method or use comprising administering a composition comprising glycopyrronium and formoterol fumarate without budesonide.

[029] In some embodiments, the present disclosure provides a method for decreasing the mortality of a subject suffering from cardiovascular disease, the method comprising administering to the subject twice daily a therapeutically effective dose comprising a composition comprising budesonide, glycopyrronium and formoterol fumarate, wherein the dose is administered to the subject via a metered dose inhaler. In some embodiments, the present disclosure provides a use of a composition comprising budesonide, glycopyrronium, and formoterol fumarate in the manufacture of a medicament for decreasing the mortality of a subject suffering from cardiovascular disease, wherein the medicament is administered twice daily with a therapeutically effective dose via a metered dose inhaler. In some embodiments, the mortality is all-cause mortality. In some embodiments, the all-cause mortality of the subject is reduced by at least about 20%, at least about 30%, or at least about 40% compared to a method or use comprising administering a composition comprising glycopyrronium and formoterol fumarate without budesonide. In some embodiments, the all-cause mortality of the subject is reduced by at least about 10% compared to a method or use comprising administering a composition comprising glycopyrronium and formoterol fumarate without budesonide.

[030] In some embodiments, the present disclosure provides a method for reducing the risk of a cardiac event in a subject having cardiovascular disease, the method comprising administering to the subject twice daily a therapeutically effective dose comprising a composition comprising budesonide, glycopyrronium and formoterol fumarate, wherein the dose is administered to the subject via a metered dose inhaler, wherein the subject is at an elevated risk of a COPD exacerbation event and cardiovascular disease. In some embodiments, the present disclosure provides a use of a composition comprising budesonide, glycopyrronium, and formoterol fumarate in the manufacture of a medicament for reducing the risk of a cardiac event in a subject

having cardiovascular disease, wherein the subject is at an elevated risk of a COPD exacerbation event and cardiovascular disease, and wherein the medicament is administered twice daily with a therapeutically effective dose via a metered dose inhaler.

BRIEF DESCRIPTION OF THE DRAWINGS

[031] **Figure 1** is a graphical representation of study design.

DETAILED DESCRIPTION OF THE EMBODIMENTS

[032] Unless otherwise defined herein, scientific and technical terms used in the present disclosure shall have the meanings that are commonly understood by one of ordinary skill in the art. Further, unless otherwise required by context, singular terms shall include pluralities and plural terms shall include the singular.

[033] The articles "a" and "an" are used herein to refer to one or to more than one (i.e., to at least one) of the grammatical object of the article. By way of example, "an element" means one element or more than one element.

[034] The use of the term "or" in the claims is used to mean "and/or," unless explicitly indicated to refer only to alternatives or the alternatives are mutually exclusive, although the disclosure supports a definition that refers to only alternatives and "and/or."

[035] As used herein, the terms "comprising" (and any variant or form of comprising, such as "comprise" and "comprises"), "having" (and any variant or form of having, such as "have" and "has"), "including" (and any variant or form of including, such as "includes" and "include") or "containing" (and any variant or form of containing, such as "contains" and "contain") are inclusive or open-ended and do not exclude additional, unrecited, elements or method steps.

[036] The use of the term "for example" and its corresponding abbreviation "e.g." means that the specific terms recited are representative examples and embodiments of the disclosure that are not intended to be limited to the specific examples referenced or cited unless explicitly stated otherwise.

[037] As used herein, "about" can mean plus or minus 10% of the provided value. Where ranges are provided, they are inclusive of the boundary values. "About" can additionally or alternately mean either within 10% of the stated value, or within 5% of the stated value, or in some cases within 2.5% of the stated value; or "about" can mean rounded to the nearest significant digit.

[038] As used herein, "between" is a range inclusive of the ends of the range. For example, a number between x and y explicitly includes the numbers x and y and any numbers that fall within x and y.

[039] As used herein, the term "active agent" includes any agent, drug, compound, composition, or other substance that may be used on, or administered to a subject, e.g., a human or animal subject, for any purpose, including therapeutic, pharmaceutical, pharmacological, diagnostic, cosmetic, and prophylactic agents and immunomodulators. The term "active agent" may be used interchangeably with the terms "drug," "pharmaceutical," "medicament," "drug substance," and "therapeutic." In some embodiments, the active agent of the present disclosure comprises albuterol and/or budesonide.

[040] As used herein, the terms "associate," "associate with," and "association" refer to an interaction or relationship between a chemical entity, composition, or structure by proximity to a surface, such as the surface of another chemical entity, composition, or structure. The association includes, for example, adsorption, adhesion, hydrogen bonding, ionic bonding and electrostatic attraction, Lifshitz-van der Waals interactions and polar interactions. As described herein, active agent particles may associate with suspending particles to form a co-suspension, where there is substantially no visible separation between the suspending particles and the active agent particles or flocculates thereof due to differences in buoyancy within a propellant.

[041] As used herein, the term "respirable" refers to particles, aggregates, drops, etc. sized such that they can be inhaled and reach the airways of the lung.

[042] As used herein, "suspending particles" refer to a material or combination of materials that is acceptable for respiratory delivery, and acts as a vehicle for active agent particles. Suspending particles interact with the active agent particles to facilitate repeatable dosing, delivery or

transport of active agent to the target site of delivery, e.g., the respiratory tract (i.e., "respirable suspending particles"). In some embodiments, the suspending particles described herein are dispersed within a suspension medium including a propellant or propellant system, and can be configured according to any shape, size or surface characteristic suited to achieving a desired suspension stability or active agent delivery performance. In some embodiments, the suspending particles are porous particles that have perforated microstructures that include a structural matrix that exhibits, defines or comprises voids, pores, defects, hollows, spaces, interstitial spaces, apertures, perforations or holes that allow the surrounding suspension medium to permeate, fill or pervade the microstructure. Exemplary suspending particles include particles that exhibit a particle size that facilitates respiratory delivery of active agent and have physical configurations suited to formulation and delivery of the stabilized suspensions as described herein.

[043] As used herein, "mass mean aerodynamic diameter" or "MMAD" refers to the aerodynamic diameter of an aerosol below which 50% of the mass of the aerosol consists of particles with an aerodynamic diameter smaller than the MMAD, with the MMAD being calculated according to monograph 601 of the United States Pharmacopeia (USP).

[044] As used herein, "optical diameter" refers to the size of a particle as measured by the Fraunhofer diffraction mode using a laser diffraction particle size analyzer equipped with a dry powder dispenser (e.g., Sympatec GmbH, Clausthal-Zellerfeld, Germany).

[045] As used herein, the term "suspension medium" refers to a substance providing a continuous phase within which active agent particles and suspending particles can be dispersed to provide a co-suspension formulation. In some embodiments, the suspension medium used in co-suspension formulations described herein includes a propellant. As used herein, the term "propellant" refers to one or more pharmacologically inert substances which exert a sufficiently high vapor pressure at normal room temperature to propel a medicament from the canister of a metered dose inhalers (MDI) to a subject on actuation of the MDI's metering valve. The term "propellant" refers to both a single propellant and to a combination of two or more different propellants forming a "propellant system."

[046] As used herein, the term "co-suspension" refers to a suspension of two or more types of particles having different compositions within a suspension medium, wherein one type of

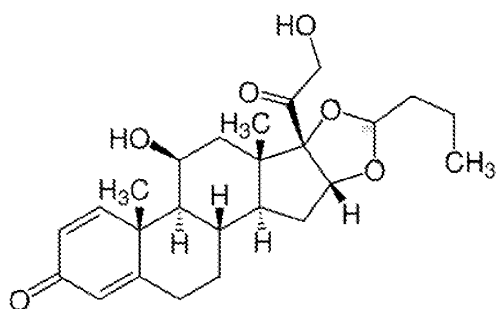
particle associates at least partially with one or more of the other particle types. Thus, the term “co-suspension” can include a suspension comprising budesonide, glycopyrronium and formoterol fumarate. The association leads to an observable change in one or more characteristics of at least one of the individual particle types suspended in the suspension medium. Characteristics modified by the association may include, for example, one or more of: the rate of aggregation or flocculation, the rate and nature of separation, i.e., sedimentation or creaming, density of a cream or sediment layer, adhesion to container walls, adhesion to valve components, and rate and the level of dispersion upon agitation. Exemplary methods for assessing whether a co-suspension is present are known to one of ordinary skill in the art, e.g., as described in WO 2010/138862.

[047] A "therapeutically effective amount" is the amount of compound, e.g., budesonide, glycopyrronium and/or formoterol fumarate as described herein, which achieves a therapeutic effect by inhibiting a condition or disorder in a patient, e.g., COPD, or by prophylactically inhibiting or preventing the onset of a condition or disorder. A therapeutically effective amount may be an amount which relieves to some extent one or more symptoms of a condition or disorder in a patient; returns to normal either partially or completely one or more physiological or biochemical parameters associated with or causative of the condition or disorder; and/or reduces the likelihood of the onset of the condition or disorder.

[048] In some embodiments, the pharmaceutical composition of the present method comprises budesonide, glycopyrronium, e.g., glycopyrronium bromide, and formoterol fumarate (i.e., BGF). In some embodiments, the budesonide, glycopyrronium, e.g., glycopyrronium bromide, and formoterol fumarate are in crystalline forms and/or micronized forms. In some embodiments, the budesonide is in micronized forms; glycopyrronium, e.g., glycopyrronium bromide, is in crystalline and micronized forms, and formoterol fumarate is in crystalline and micronized forms. In some embodiments, the pharmaceutical composition is administered to the subject in a dose of about 320 µg budesonide, 18 µg of glycopyrronium bromide and 9.6 µg of formoterol fumarate twice daily. The comparator pharmaceutical compositions of a dual therapy of glycopyrronium and formoterol fumarate (i.e., GFF), the preparations thereof, the metered dose inhalers and the method of use thereof are described in WO 2010/138862, WO 2010/138868 and WO 2010/138884, the content of which are hereby incorporated by reference in their entireties.

for all purposes. In one example, the GFF treatment comprises administering BEVESPI® AEROSPHERE to a patient suffering from COPD.

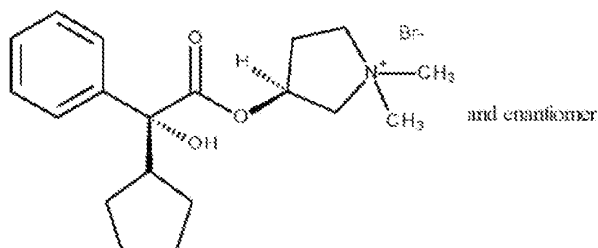
[049] As used herein, "budesonide" refers to a corticosteroid with the chemical names (RS)-11 β ,21-dihydroxy-16 α ,17 α -(butylidenebis(oxy))pregna-1,4-diene-3,20-dione and (RS)-11 β ,16 α ,17,21-Tetrahydroxypregna-1,4-diene-3,20-dione cyclic 16,17 acetal with butyraldehyde. The molecular formula of Budesonide is C₂₅H₃₄O₆ and the molecular weight of Budesonide is 430.54 g/mol. Budesonide contains nine chiral centers and, in some embodiments, the budesonide is provided as a mixture of the (22R) and (22S) epimers of budesonide. In some embodiments, budesonide is provided as a racemate (1:1 mixture) of the two epimers (22R and 22S). In some embodiments, the chemical structure of budesonide is represented as follows (* indicating stereocenter):



[050] Budesonide is an anti-inflammatory corticosteroid that exhibits potent glucocorticoid and weak mineralocorticoid activity and is approved worldwide in orally inhaled formulations for treatment of asthma and chronic obstructive pulmonary disease (COPD), both as a mono-product and in combination with formoterol and /or glycopyrrolate, for individuals with pulmonary diseases and/or disorders.

[051] Glycopyrrolate is a quaternary ammonium salt with the following chemical name: (RS)-[3-(SR)Hydroxy-1,1-dimethylpyrrolidinium bromide] α -cyclopentylmandelate. The molecular formula is C₁₉H₂₈BrNO₃, and the molecular weight is 398.33 g/mol. Glycopyrrolate contains two chiral centers and, in some embodiments, is provided as a mixture of the R,S and S,R diastereomers. In some embodiments, glycopyrrolate is provided as a racemate (1:1 mixture) of

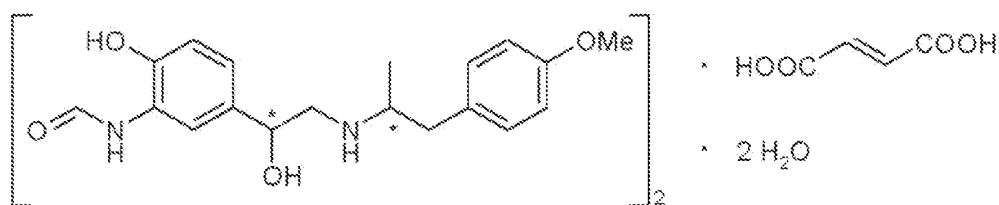
the R,S and S,R diastereomers. In some embodiments, the chemical structure of glycopyrrolate is represented as follows:



[052] The active moiety of glycopyrrolate is “glycopyrronium.” Glycopyrronium is the positively charged ion of glycopyrrolate. In some embodiments, the terms “glycopyrrolate” and “glycopyrronium bromide” are used interchangeably. Thus, as used herein, use of the term glycopyrronium in some instances would encompass glycopyrronium bromide, i.e., glycopyrrolate.

[053] Glycopyrrolate is a long-acting antimuscarinic agent which is often referred to as an anticholinergic. It has similar affinity to the subtypes of muscarinic receptors M1 to M5. In the airways, it exhibits pharmacological effects through inhibition of the M3 receptor at the smooth muscle leading to bronchodilation. The bronchodilation following inhalation of glycopyrrolate is predominantly a site-specific effect.

[054] Formoterol fumarate has the chemical name N-[2-Hydroxy-5-[(1RS)-1-hydroxy-2-(4-methoxyphenyl)-1-methylethyl]-amino]ethyl]phenyl]formamide, (E)-2-butenedioate dihydrate. The molecular formula of formoterol fumarate is $(C_{19}H_{24}N_2O_4)_2 \cdot C_4H_4O_4 \cdot 2H_2O$ and the molecular weight of formoterol fumarate is 840.91 g/mol. In some embodiments, the chemical structure of formoterol fumarate is represented as follows:



[055] Formoterol fumarate is a long-acting selective beta₂-adrenergic agonist (beta₂-agonist) with a rapid onset of action. Inhaled formoterol fumarate acts locally in the lung as a bronchodilator. Although beta₂-receptors are the predominant adrenergic receptors in bronchial smooth muscle and beta₁-receptors are the predominant receptors in the heart, there are also beta₂-receptors in the human heart comprising 10% to 50% of the total beta-adrenergic receptors. The precise function of these receptors has not been established, but they raise the possibility that even highly selective beta₂-agonists may have cardiac effects.

[056] The method of the present disclosure can use various ratios of budesonide, glycopyrronium, e.g., glycopyrronium bromide, and formoterol fumarate. In some embodiments, the composition comprises budesonide and glycopyrronium at a ratio of about 5:1 to about 30:1 (wt/wt), about 10:1 to about 25:1 (wt/wt), about 15:1 to about 20:1 (wt/wt), about 16:1 to about 19:1 (wt/wt), about 17.5:1 (wt/wt), about 17.6:1 (wt/wt), about 17.7:1 (wt/wt), about 17.8:1 (wt/wt), about 17.9:1 (wt/wt), about 18:1 (wt/wt), about 18.1:1 (wt/wt), about 18.2:1 (wt/wt), about 18.3:1 (wt/wt), about 18.4:1 (wt/wt) or about 18.5:1 (wt/wt).

[057] In some embodiments, the composition comprises budesonide and formoterol fumarate at a ratio of about 20:1 to about 50:1, about 25:1 to about 45:1, about 30:1 to about 40:1, about 32:1 to about 35:1, about 33:1, about 33.1:1, about 33.2:1, about 33.3:1, about 33.4:1, about 33.5:1, about 33.6:1, about 33.7:1, about 33.8:1, about 33.9:1 or about 34:1.

[058] In some embodiments, the budesonide, glycopyrronium and formoterol fumarate are in the form of particles, wherein at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95% or about 100% of the particles by volume comprise an optical diameter of about 0.1 µm to about 20 µm, about 0.5 µm to about 10 µm, or about 1 µm to about 7 µm.

[059] In some embodiments, the composition comprises composition comprises micronized particles of budesonide. In some embodiments, the composition comprises composition comprises micronized particles of glycopyrronium. In some embodiments, the composition comprises composition comprises micronized particles of formoterol fumarate. In some embodiments, each of budesonide, glycopyrronium and formoterol fumarate are micronized.

[060] In some embodiments, the composition comprises a plurality of budesonide particles, a plurality of glycopyrronium particles, a plurality of formoterol fumarate particles, a plurality of respirable suspending particles, and a suspension medium, wherein the plurality of budesonide particles, the plurality of glycopyrronium particles, the plurality of formoterol fumarate particles and the plurality of suspending particles are co-suspended in the suspension medium to form a co-suspension.

[061] In some embodiments, the suspension medium is a pharmaceutically acceptable propellant selected from a hydrofluoroalkane (HFA) propellant, a hydrofluoroolefins (HFO) propellant, a hydrofluorocarbon propellant (HFC), and combination thereof. In some embodiments, the suspension medium is a propellant of pharmaceutical grade (1E)-1,3,3,3-Tetrafluoro-1-propene (HFO-1234ze(E)).

[062] In some embodiments, the respirable suspending particles comprise a phospholipid or other respirable suspending particles known in the art. In some embodiments, the phospholipid is 1,2-Distearoyl-sn-glycero-3-phosphocholine (DSPC).

[063] In some embodiments, the respirable suspending particles comprise a volume median optical diameter of about 0.1 μm to about 100 μm or about 0.2 μm to about 50 μm . In some embodiments, the respirable suspending particles are about 0.1mg/mL to about 100mg/mL, about 1 mg/mL to about 30 mg/mL, about 2 mg/mL to about 20 mg/mL, or about 4 mg/mL to about 15 mg/mL in the suspension medium. In some embodiments, the respirable suspending particle is perforated.

[064] In some embodiments, a weight ratio of total mass of the respirable suspending particles to total mass of the budesonide, glycopyrronium and formoterol fumarate particles is about 1:2 to about 500:1, about 1:1 to about 300:1, about 1.5:1 to about 200:1, about 1:10 to about 10:1, about 10:1 to about 100:1, or about 50:1 to about 200:1.

[065] As described in relation to the methods provided herein, the composition comprising budesonide, glycopyrronium, e.g., glycopyrronium bromide, and formoterol fumarate described herein may be used in a metered dose inhaler (MDI) system. MDIs are configured to deliver a specific amount of a medicament in aerosol form. In some embodiments, an MDI system

includes a pressurized, liquid phase formulation-filled canister or cartridge disposed in an actuator formed with a mouthpiece. The MDI system may include the formulations described herein, which include a suspension medium, at least one species of active agent particles and at least one species of suspending particles. The canister or cartridge used in the MDI be any of any suitable configuration, and in one exemplary embodiment, the canister or cartridge may have a volume ranging from about 5 mL to about 25 mL, such as, for example a canister or cartridge having a 8 mL to 22 mL, a 10 mL to 20 mL or a 15 mL to 20 mL volume. After shaking the device, the mouthpiece is inserted into a subject's mouth between the lips and teeth. The subject typically exhales deeply to empty the lungs and then takes a slow deep breath while actuating the MDI cartridge.

[066] Persons having ordinary skill in the art will understand that priming prior to use may be necessary to ensure that the MDI delivers the correct amount of the medicament, and that priming comprises first shaking and then actuating the inhaler away from the subject before use.

[067] When actuated, the specified volume of formulation travels to the expansion chamber, out the actuator nozzle and into a high-velocity spray that is drawn into the lungs of a patient. In some embodiments, the dose of active agent, i.e., budesonide, glycopyrronium and formoterol fumarate, delivered throughout emptying of an MDI canister or cartridge is not more than 20% greater than the mean delivered dose and is not less than 20% less than the mean delivered dose. In some embodiments, the dose of active agent, i.e., budesonide, glycopyrronium and formoterol fumarate, delivered throughout emptying of an MDI canister is not more than 15% greater or less than the mean delivered dose. In some embodiments, the dose of active agent, i.e., budesonide, glycopyrronium and formoterol fumarate, delivered throughout emptying of an MDI canister or cartridge is not more than 10% greater or less than the mean delivered dose.

[068] In some embodiments, inside an exemplary cannister or cartridge is a metering valve including a metering chamber capable of holding a defined volume of the formulation (e.g., 40 μ L to 80 μ L) or any other suitable volume available in commercially available metering valves), which is released into an expansion chamber at the distal end of the valve stem when actuated. The actuator retains the canister and may also include a port with an actuator nozzle for receiving the valve stem of the metering valve. When actuated, the specified volume of formulation travels

to the expansion chamber, out the actuator nozzle and into a high-velocity spray that is drawn into the lungs of a subject.

[069] In some embodiments, the metered dose inhaler is a hydrofluoroalkane (HFA 134a) propelled pressurized metered dose inhaler containing 28 or 120 inhalations. In some embodiments, the canister or cartridge of the metered dose inhaler has an attached dose indicator and is supplied with a white plastic actuator body and mouthpiece with a light grey dust cap.

[070] In some embodiments, after priming, each metered dose, i.e., actuation, of the inhaler can provide 182 µg of budesonide, 10.4 µg of glycopyrrolate (equivalent to 8.2 µg of glycopyrronium), and 5.5 µg of formoterol fumarate (equivalent to 4.7 µg of formoterol) from the valve which delivers 160 µg of budesonide, 9.0 µg of glycopyrrolate (equivalent to 7.2 µg of glycopyrronium), and 4.8 µg of formoterol fumarate (equivalent to 4.1 µg of formoterol) from the actuator. The actual amount of drug delivered to the lung may depend on patient factors, such as the coordination between actuation of the device and inspiration through the delivery system.

[071] In some instances, one dose shall be defined as two metered doses, i.e., actuations, wherein each metered dose is achieved through a single inhalation of a single actuation of the MDI.

[072] Exemplary MDIs and methods of use thereof are further described, e.g., in WO 2010/138862, WO 2010/138868, and WO 2010/138884.

[073] In some embodiments, the pharmaceutical composition comprises budesonide, glycopyrronium and formoterol fumarate (BGF). In some embodiments, the pharmaceutical composition is administered to the patient at a dosage of 320 µg of budesonide, 18 µg of glycopyrronium bromide and 9.6 µg of formoterol fumarate twice daily.

[074] In some embodiments, the pharmaceutical composition is administered via a metered dose inhaler (MDI). MDIs are configured to deliver a specific amount of a medicament in aerosol form. In some embodiments, an MDI includes a pressurized, liquid phase formulation-filled canister and/or cartridge disposed in an actuator formed with a mouthpiece. The MDI contains the pharmaceutical composition described herein. The canister or cartridge used in the MDI may be any of any suitable configuration. After shaking the device, the mouthpiece is inserted into a

patient's mouth between the lips and teeth. The patient typically exhales deeply to empty the lungs and then takes a slow deep breath while actuating the inhaler.

[075] In some embodiments, the pharmaceutical composition also comprises suspending particles. In some embodiments, the suspending particles comprise porous particles that form a co-suspension with the drug crystals. In some embodiments, the suspending particles comprising 1,2-Distearoyl-sn-Glycero-3-Phosphocholine (DSPC) have perforated microstructures that include a structural matrix that exhibits, defines or comprises voids, pores, defects, hollows, spaces, interstitial spaces, apertures, perforations or holes that allow the surrounding suspension medium to permeate, fill or pervade the microstructure. The suspending particles are suitable for respiratory delivery and act as a vehicle for active agent particles.

[076] Examples of the pharmaceutical compositions, the preparations thereof, the metered dose inhalers and the method of use thereof are described in WO 2010/138862, WO 2010/138868 and WO 2010/138884, the content of which are hereby incorporated by reference in their entireties for all purposes. In some embodiments, the present method or use reduces the all-cause mortality of the patient as compared with a patient suffering from COPD receiving a treatment of glycopyrrolate and formoterol (GFF). In some embodiments, the treatment of glycopyrrolate and formoterol comprises administering to the patient an effective amount of a pharmaceutical composition deliverable from a metered dose inhaler comprising glycopyrrolate and formoterol (GFF).

[077] In the present disclosure, a therapeutically effective dose of a composition comprising budesonide, glycopyrronium, and formoterol fumarate are administered to a subject. The term "dose" refers to the amount of the composition administered at a given time, e.g., within 30 minutes, to a subject. A "metered dose" or an "actuation of the MDI" refers to the amount of the composition which is expelled from the inhaler upon one actuation. For example, when administered via a metered dose inhaler, the dose could comprise several metered doses (or actuations) which are expelled from the inhaler. In one example, a subject can be administered two daily doses, e.g., once in the morning and once in the evening, and in the morning dose, two metered doses are administered, and in the evening, two additional metered doses are administered.

[078] In some embodiments, the method of the present disclosure comprises administering to the subject one or more metered doses from the MDI through inhalation, wherein the dose administered comprises about 150 µg to about 500 µg, about 200 µg to about 450 µg, about 220 µg to about 420 µg, about 270 µg to about 370 µg, about 300 µg to about 340 µg, or about 320 µg budesonide.

[079] In some embodiments, the method of the disclosure comprises administering to the subject a dose (i.e., one or more metered doses) from the MDI through inhalation, wherein the dose administered comprises about 2 µg to about 40 µg, about 5 µg to about 35 µg, about 10 µg to about 25 µg, about 15 µg to about 20 µg, about 16 µg to about 19 µg, about 17 µg to about 19 µg or about 17.5 µg to about 18.5 µg glycopyrronium bromide. In some embodiments, the method of the disclosure comprises administering to the subject a dose (i.e., one or more metered doses) from the MDI through inhalation, wherein the dose administered comprises about 18 µg glycopyrronium bromide. In some embodiments, the method of the disclosure comprises administering to the subject a dose (i.e., one or more metered doses) from the MDI through inhalation, wherein the dose administered comprises about 2 µg to about 40 µg, about 5 µg to about 35 µg, about 10 µg to about 20 µg, about 12 µg to about 16 µg, about 13 µg to about 15 µg, or about 14 µg to about 15 µg glycopyrronium. In some embodiments, the method of the disclosure comprises administering to the subject a dose (i.e., one or more metered doses) from the MDI through inhalation, wherein the dose administered comprises 14.4 µg glycopyrronium.

[080] In some embodiments, the method of the disclosure comprises administering to the subject a dose (i.e., one or more metered doses) from the MDI through inhalation, wherein the dose administered comprises about 1 µg to about 25 µg, about 2 to about 20 µg, about 5 to about 15 µg, about 8 to about 12 µg, about 9 µg to about 11 µg, or about 9 to about 10 µg formoterol fumarate. In some embodiments, the method of the disclosure comprises administering to the subject a dose (i.e., one or more metered doses) from the MDI through inhalation, wherein the dose administered comprises about 9.6 µg formoterol fumarate.

[081] In some embodiments, the method of the disclosure comprises administering to the subject a dose (i.e., one or more metered doses) from the MDI through inhalation, wherein the dose administered comprises about 150 ug to 500 µg budesonide, about 2 ug to about 40 µg

glycopyrronium bromide, and about 1 ug to about 25 µg formoterol fumarate. In some embodiments, the method of the disclosure comprises administering to the subject a dose (i.e., one or more metered doses) from the MDI through inhalation, wherein the dose administered comprises about 220 ug to about 420 µg budesonide, about 5 to about 35ug glycopyrronium bromide, and about 2 ug to about 20 µg formoterol fumarate. In some embodiments, the method of the disclosure comprises administering to the subject a dose (i.e., one or more metered doses) from the MDI through inhalation, wherein the dose administered comprises about 270 to about 370 µg budesonide, about 10 to about 25ug glycopyrronium bromide, and about 5 to about 15 µg formoterol fumarate. In some embodiments, the method of the disclosure comprises administering to the subject a dose (i.e., one or more metered doses) from the MDI through inhalation, wherein the dose administered comprises about 300 ug to about 340 µg budesonide, about 15 ug to about 20 ug glycopyrronium bromide, and about 8 ug to about 12 µg formoterol fumarate. In some embodiments, the method of the disclosure comprises administering to the subject a dose (i.e., one or more metered doses) from the MDI through inhalation, wherein the dose administered comprises about 320 µg budesonide, about 18 µg glycopyrronium bromide, and about 9.6 µg formoterol fumarate.

[082] In some embodiments, the method comprises administering to the subject the composition in 1 metered dose via inhalation in a 24 hour period. In some embodiments, the method comprises administering to the subject 2 metered doses via inhalation in a 24 hour period. In some embodiments, the method comprises administering to the subject 3 metered doses via inhalation in a 24 hour period. In some embodiments, the method comprises administering to the subject 4 metered doses via inhalation in a 24 hour period. In some embodiments, the method comprises administering to the subject 5 metered doses via inhalation in a 24 hour period. In some embodiments, the method comprises administering to the subject 6 metered doses via inhalation in a 24 hour period. In some embodiments, the method comprises administering to the subject 7 metered doses via inhalation in a 24 hour period. In some embodiments, the method comprises administering to the subject 8 metered doses via inhalation in a 24 hour period. In some embodiments, the method comprises administering to the subject 9 metered doses via inhalation in a 24 hour period. In some embodiments, the method comprises administering to the subject 10 metered doses via inhalation in a 24 hour period. In some embodiments, no more than 8 metered doses are administered to the subject in a 24 hour period.

In some embodiments, no more than 6 metered doses are administered to the subject in a 24 hour period.

[083] In some embodiments, the method comprises administering to the subject via inhalation 1 dose per day, wherein the dose comprises 2 metered doses, wherein the two inhaled metered doses are delivered in quick succession. In some embodiments, the phrase “quick succession” when referring to administration of two metered doses means that the second metered dose is inhaled within about 30 seconds, about 1 minute, about 2 minutes, about 5 minutes, about 10 minutes, about 15 minutes or about 30 minutes of the first metered dose. In some embodiments, the method comprises administering to the subject via inhalation 2 doses per day, wherein each dose comprises 2 metered doses, wherein the two inhaled metered doses are delivered in quick succession. In some embodiments, the method comprises administering to the subject via inhalation 3 doses per day, wherein each dose comprises 2 metered doses delivered in quick succession. In some embodiments, the method comprises administering to the subject via inhalation 4 doses per day, wherein each dose comprises 2 metered doses delivered in quick succession. In some embodiments, no more than 4 doses of 2 inhaled metered doses are administered to the subject in a 24 hour period. In some embodiments, no more than 3 doses of 2 inhaled metered doses are administered to the subject in a 24 hour period.

[084] In some embodiments, the administering comprises delivering one or more metered doses from the MDI to the subject through inhalation, wherein the total daily delivered dose is about 200 ug to about 1600 µg budesonide, about 5 to about 100 µg glycopyrronium bromide and about 5 ug to about 50 µg formoterol fumarate. The term “total daily delivered dose” refers to the cumulative amount of active agent, e.g., budesonide, glycopyrronium bromide and formoterol fumarate, delivered in a 24 hour period, independent of the number doses (and metered doses) administered. In some embodiments, the total daily delivered dose is about 300 ug to about 1300 µg budesonide, about 15 ug to about 80 µg glycopyrronium bromide, and about 9 ug to about 40 µg formoterol fumarate. In some embodiments, the total daily delivered dose is about 300 ug to about 1000 µg budesonide, about 15 ug to about 60 µg glycopyrronium bromide, and about 9 ug to about 30 µg formoterol fumarate. In some embodiments, the total daily delivered dose is about 600 ug to about 1000 µg budesonide, about 30 ug to about 60 µg glycopyrronium bromide, and about 15 ug to about 30 µg formoterol fumarate.

[085] In some embodiments, about 40 µg to about 250 µg budesonide is delivered per metered dose to the subject. In some embodiments, about 50 µg to about 200 µg budesonide is delivered per metered dose to the subject. In some embodiments, about 75 µg to about 175 µg budesonide is delivered per metered dose to the subject. In some embodiments, about 80 µg to about 160 µg budesonide is delivered per metered dose to the subject. In some embodiments, about 40 µg to about 120 µg budesonide is delivered per metered dose to the subject. In some embodiments, about 60 µg to about 100 µg budesonide is delivered per metered dose to the subject. In some embodiments, about 120 µg to about 200 µg budesonide is delivered per metered dose to the subject. In some embodiments, about 140 µg to about 180 µg budesonide is delivered per metered dose to the subject. In some embodiments, about 60 µg, about 70 µg, about 80 µg, about 90 µg, about 100 µg, about 110 µg, about 120 µg, about 130 µg, about 140 µg, about 150 µg, about 160 µg, about 170 µg, about 180 µg, about 190 µg, or about 200 µg budesonide is delivered per metered dose to the subject. In some embodiments, about 160 µg budesonide is delivered per metered dose.

[086] In some embodiments, about 2 µg to about 20 µg glycopyrronium is delivered per metered dose to the subject. In some embodiments, about 3 µg to about 15 µg glycopyrronium is delivered per metered dose to the subject. In some embodiments, about 4 µg to about 12 µg glycopyrronium is delivered per metered dose to the subject. In some embodiments, about 5 µg to about 10 µg glycopyrronium is delivered per metered dose to the subject. In some embodiments, about 6 µg to about 8 µg glycopyrronium is delivered per metered dose to the subject. In some embodiments, about 6 µg, about 7 µg, about 7.1 µg, about 7.2 µg, about 7.3 µg, about 7.4 µg, about 7.5 µg, about 7.6 µg, about 7.7 µg, or about 7.8 µg, glycopyrronium is delivered per metered dose to the subject. In some embodiments, about 7.4 µg glycopyrronium is delivered per metered dose.

[087] In some embodiments, about 1 µg to about 15 µg formoterol fumarate is delivered per metered dose to the subject. In some embodiments, about 1.5 µg to about 10 µg formoterol fumarate is delivered per metered dose to the subject. In some embodiments, about 2 µg to about 6 µg formoterol fumarate is delivered per metered dose to the subject. In some embodiments, about 3 µg to about 5 µg formoterol fumarate is delivered per metered dose to the subject. In some embodiments, about 4 µg to about 5 µg formoterol fumarate is delivered per metered dose

to the subject. In some embodiments, about 4.5 µg, about 4.6 µg, about 4.7 µg, about 4.8 µg, about 4.9 µg, about 5 µg, about 5.1 µg, or about 5.2 µg formoterol fumarate is delivered per metered dose to the subject. In some embodiments, about 4.8 µg formoterol fumarate is delivered per metered dose.

[088] In some embodiments, the methods described herein are directed to a subject at elevated risk of a COPD event and cardiovascular disease. Upon treatment with the present methods, subjects having elevated risks of both COPD event and cardiovascular disease unexpectedly can (i) reduce risk of a severe COPD event by at least about 10%, (ii) reduce risk of a severe cardiac event by at least about 10%, or (iii) reduces risk of a severe COPD event by at least about 10% and reduces risk of a severe cardiac event by at least about 10%; as compared to administration of a composition comprising a same dose of glycopyrronium and formoterol fumarate but no budesonide. The disclosure notes that previous methods of administering the triple therapy of budesonide, glycopyrronium and formoterol fumarate did not appreciate that the subpopulation of subjects with elevated risks of both COPD event and cardiovascular disease can show unexpected improvement in the primary endpoint: time to first severe cardiac or COPD event. In some embodiments, this primary end point is a composite end point comprising time to the (1) first HF acute healthcare visit/hospitalization, (2) MI hospitalization, (3) severe COPD exacerbation, or (4) cardiopulmonary death.

[089] In some embodiments, the subject of the disclosed method is an individual with COPD, either male or female between 40 to 80 years of age, who is at elevated risk of a COPD exacerbation event and elevated risk of cardiovascular disease. In some embodiments, the diagnosis of COPD in the subject is confirmed by a post-bronchodilator FEV₁/FVC < 70%. In some instances, the subject is a current or former smoker with a history of ≥ 10 pack-years of cigarette smoking. In some instances, the subject has a blood eosinophil count of ≥ 100 cells/mm³.

[090] In some embodiments, the subject is administered a COPD Assessment Test™ (CAT) to determine the existence of COPD, which includes an inquiry as to the frequency of cough, the severity of phlegm, the tightness of the chest, the ability to walk an incline without becoming breathless, the ability to do home chores, the confidence in leaving the house, sleep quality and

energy levels. Persons having ordinary skill in the art will understand that the CAT is a questionnaire for individuals with COPD designed to assess the severity of COPD and how it changes over time. In some embodiments, the subject has a CAT score of ≥ 10 . In some embodiments, the subject has a phlegm and/or cough CAT sub-score ≥ 2 .

[091] In some embodiments, the subject is an individual at risk of cardiovascular disease, which would include an individual already with cardiovascular disease. In some embodiments, the subject is an individual having severe cardiovascular disease or at risk of severe cardiovascular disease. In some embodiments, cardiovascular disease and risk factors therefor can include: angina pectoris with objective evidence of myocardial ischemia (e.g., on treadmill testing, myocardial infarction, percutaneous coronary intervention, coronary artery bypass grafting, objective findings of coronary stenosis ($\geq 50\%$) in at least two coronary arteries involving the main vessel, a major branch, or a bypass graft, chronic heart failure with New York Heart Association (NYHA) class II-III functional limitation, and/or peripheral arterial disease, where peripheral arterial disease can include peripheral arterial intervention, stenting surgical revascularization, lower extremity amputation as a result of peripheral arterial obstructive disease, current symptoms of intermittent claudication, documented ankle/brachial index < 90 , and/or angiographic evidence of peripheral artery disease.

[092] In some embodiments, the subject has a documented history of hypertension. In some embodiments, hypertension is defined as a documented history of a blood pressure (BP) over 140/90 mmHg with both an elevated systolic BP (> 140 mmHg) and an elevated diastolic BP (> 90 mmHg). In some embodiments, the subject is receiving at least one anti-hypertensive therapy that has been prescribed by a physician for lowering blood pressure.

[093] In some embodiments, the subject has diabetes mellitus. In some embodiments, the subject has chronic kidney disease with eGFR > 20 mL/min/1.73m² and < 60 mL/min/1.73m². In some embodiments, the subject has dyslipidemia. In some embodiments, subjects are considered to exhibit dyslipidemia if they have an LDL-C > 130 mg/dL (3.36 mmol/L) and/or an HDL-C < 40 mg/dL (1.03 mmol/L) for men or < 50 mg/dL (1.29 mmol/L) for women. In some embodiments, subjects are considered to exhibit dyslipidemia if they have been prescribed a lipid

lowering therapy prescribed by a physician for hypercholesterolemia. In some embodiments, hypercholesterolemia is defined in subjects having LDL-C >130 mg/dL (3.36 mmol/L).

[094] In some embodiments, the risk of cardiovascular disease is determined using an established cardiovascular risk assessment tool. In some embodiments, the subject has a Q-RISK-3 score of greater than about 20%. In some embodiments, the subject has an atherosclerotic cardiovascular disease (ASCVD) risk equation score of greater than about 20%, as calculated by the American College of Cardiology method. In some embodiments, the subject has a Framingham Risk Score of greater than about 20%. In some embodiments, subjects under the age of about 50 have a SCORE2 tool score of greater than about 7.5%. In some embodiments, subjects between the ages of about 50 and about 69 have a SCORE2 tool score of greater than about 10%. In some embodiments, subjects over the age of about 70 have a SCORE2-OP tool score greater than about 15%. In some embodiments, other cardiovascular risk assessment tools are known in the art and can be used.

[095] In some embodiments, the subject may exhibit moderate to severe/heavy coronary artery calcification score. In some embodiments, coronary artery calcification is assessed by the Agatston score, wherein a score of about 101 to about 1000 indicates moderate coronary artery calcification, and wherein a score of greater than about 1000 indicates severe/heavy coronary artery calcification.

[096] In some embodiments, the methods described herein can reduce the risk of a severe COPD event or cardiac event. In some embodiments, the phrase “reduce the risk of severe COPD event” can include time to first severe COPD event, wherein a COPD event comprises hospitalization for COPD or death due to COPD.

[097] In some embodiments, the phrase “reduce the risk of cardiac event” is determined by measuring the time to a cardiac event, e.g., heart failure, myocardial infarction, cardiac death, relative to subjects being administered a composition comprising a same dose of glycopyrronium and formoterol fumarate but no budesonide. The composite primary efficacy endpoint of the methods described herein is time to first severe cardiac or COPD event, wherein a severe cardiac or COPD event comprises (i) heart failure (HF) acute healthcare visit/hospitalization, (ii) myocardial infarction (MI) hospitalization, (iii) severe COPD exacerbation, and/or (iv)

cardiopulmonary death relative to subjects being administered a composition comprising a same dose of glycopyrronium and formoterol fumarate but no budesonide.

[098] Secondary endpoints may include (i) time to first severe COPD exacerbation event, wherein a COPD exacerbation event comprises hospitalization for COPD or death due to COPD; (ii) time to first severe cardiac event, wherein a severe cardiac event comprises cardiac death, non-fatal HF acute healthcare visit/hospitalization, or non-fatal MI hospitalization; (iii) time to cardiopulmonary death; (iv) rate of moderate to severe COPD exacerbation; (v) time to MI hospitalization or cardiac death; and/or (vi) time to HF acute healthcare visit/hospitalization or cardiac death. In some embodiments, the method reduces the risk of heart failure (HF) acute healthcare visit/hospitalization by at least 5%, 10%, 15%, 20%, 25%, 30%, 40%, or greater than 40%. In some embodiments, the method reduces the risk of myocardial infarction (MI) hospitalization by at least 5%, 10%, 15%, 20%, 25%, 30%, 40%, or greater than 40%. In some embodiments, the method reduces the risk of severe COPD exacerbation by at least 5%, 10%, 15%, 20%, 25%, 30%, 40%, or greater than 40%. In some embodiments, the method reduces the risk of cardiopulmonary death by at least 5%, 10%, 15%, 20%, 25%, 30%, 40%, or greater than 40%.

[099] Tertiary or exploratory endpoints may include (i) time to all-cause mortality; (ii) time to first cardiovascular event including stroke/TIA, unstable angina, CV haemorrhage, and/or CV events from elective procedures; and/or (iii) hospitalizations, emergency room visits, unplanned out-patient visits, and urgent healthcare visits. In some embodiments, the method reduces the risk of time to all-cause mortality by at least 5%, 10%, 15%, 20%, 25%, 30%, 40%, or greater than 40%. In some embodiments, the method reduces the time to first cardiovascular event including stroke/TIA, unstable angina, CV haemorrhage, and/or CV events from elective procedures by at least 5%, 10%, 15%, 20%, 25%, 30%, 40%, or greater than 40%. In some embodiments, the method reduces hospitalizations, emergency room visits, unplanned out-patient visits, and urgent healthcare visits by at least 5%, 10%, 15%, 20%, 25%, 30%, 40%, or greater than 40%.

[0100] Safety endpoints may include serious adverse events (SAEs), discontinuation adverse events (DAEs), and/or adverse events of special interest (AESI) of pneumonia leading to hospitalization or death.

[0101] In some embodiments, severe cardiac events are defined as per the Hicks criteria, modified to capture only cardiac events. Hicks et al., “2017 Cardiovascular and Stroke Endpoint Definitions for Clinical Trials.” *Circulation*, 27;137(9):961-972 (2018).

[0102] In some embodiments a severe cardiac event may comprise a myocardial infarction. In some embodiments a severe cardiac event may comprise procedures to treat an acute myocardial infarction (AMI), including but not limited to percutaneous coronary intervention and coronary artery bypass graft surgery. In some embodiments, a severe cardiac event does not comprise events due to elective coronary procedures to treat chronic stable angina.

[0103] In some embodiments a severe cardiac event may comprise heart failure, acute care visits and/or hospitalizations as defined by the Abraham criteria. Abraham et al., “Standardized definitions for evaluation of heart failure therapies: scientific expert panel from the heart failure collaboratory and academic research consortium.” *Eur J Heart Fail*, 22:2175-2186 (2020). In some embodiments, a severe cardiac event does not comprise scheduled administration of heart failure therapies of procedure, such as intravenous (IV) diuretics, IV vasoactive agents, or mechanical fluid removal.

[0104] In some embodiments, cardiac or cardiopulmonary deaths include deaths due to AMI (as defined above, deaths due to procedures to treat an AMI, sudden cardiac death, and death due to heart failure. In some embodiments cardiac or cardiopulmonary deaths do not include death due to stroke, death due to cardiovascular procedures (except to treat an AMI), deaths due to cardiovascular hemorrhage, and deaths due to any other cardiovascular causes. In some embodiments, these deaths which are not included as cardiac or cardiopulmonary deaths are included as exploratory cardiovascular events.

[0105] In some embodiments, moderate and severe COPD exacerbations are defined as per standards set by the Global Initiative for Chronic Obstructive Lung Disease (GOLD). In some embodiments, pneumonia is defined as hospitalized pneumonia with radiological evidence. In

some embodiments, pulmonary events may not comprise pulmonary malignancies or other non-related conditions. In some embodiments, episodes of pneumonia that lead to hospitalization or death that occurs more than about 5 days after admission are adjudicated as COPD without pneumonia to exclude episodes of pneumonia that are secondary complications of a COPD exacerbation, such as ventilator- or healthcare-related pneumonias.

[0106] In some embodiments, cardiovascular events for exploratory analysis include deaths and non-fatal events that are not cardiac in nature and are therefore excluded from the modified Hicks definition of myocardial infarctions and cardiac deaths (strokes, TIAs, procedural events not conducted to treat an AMI). In some embodiments, cardiovascular events for exploratory analysis include other serious cardiac events not captured in the primary or secondary endpoint definitions. In some embodiments, cardiovascular events for exploratory analysis include unstable angina requiring hospitalization. In some embodiments, a MedDRA query defines and identifies searches of exploratory cardiac events and arrhythmias.

[0107] In some embodiments, the method reduces risk of a severe COPD exacerbation event by at least about 10%, about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, about 50%, about 60%, about or about 70% as compared to administration of a composition comprising a same dose of glycopyrronium and formoterol fumarate but no budesonide. In some embodiments, the method reduces risk of a severe cardiac event by at least about 10%, about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70% as compared to administration of a composition comprising a same dose of glycopyrronium and formoterol fumarate but no budesonide.

[0108] In some embodiments, the method increases the time to first major adverse cardiovascular events (MACE) event. The term MACE can include acute myocardial infarction (AMI), stroke, and cardiovascular mortality. In some embodiments, the method increases the time to MACE in a subject by at least about 10%, about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70% as compared to administration of a composition comprising a same dose of glycopyrronium and formoterol fumarate but no budesonide

[0109] In some embodiments, the method increases the time to cardiopulmonary death. In some embodiments, the method increases the time to cardiopulmonary death in a subject by at least about 10%, about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70% as compared to administration of a composition comprising a same dose of glycopyrronium and formoterol fumarate but no budesonide.

[0110] In some embodiments, the method reduces risk of a COPD exacerbation event by at least about 10% and reduces the risk of a severe cardiac event by at least about 10% as compared to administration of a composition comprising a same dose of glycopyrronium and formoterol fumarate but no budesonide.

[0111] In some embodiments, the method provides an annualized severe COPD exacerbation event rate at least about 15% lower, or at least about 25% lower as compared to administration of a composition comprising a same dose of glycopyrronium and formoterol fumarate but no budesonide. In some embodiments, the method provides an annualized severe cardiac event rate at least about 15% lower, or at least about 25% lower, as compared to administration of a composition comprising a same dose of glycopyrronium and formoterol fumarate but no budesonide.

[0112] In some embodiments, the subject's forced expiratory volume in 1 second area under the curve from 0-6 hours (FEV_1 AUC₀₋₆) at 12 weeks following the start of the methods as described herein comprising administration of the composition is greater than about 90mL, greater than about 95mL, greater than about 100mL, greater than about 105mL, greater than about 110 mL, greater than about 115mL, greater than about 120mL, greater than about 125mL or greater than about 130mL.

[0113] In some embodiments, following the start of the methods as described herein, the subject's trough FEV_1 at 12 weeks following administration of the composition is greater than about 70mL, greater than about 75mL, greater than about 80mL, greater than about 85mL, greater than about 90mL, greater than about 95mL, greater than about 100mL, greater than about 105mL or greater than about 110mL.

[0114] In some embodiments, the subject's trough FEV₁ at 12 weeks following administration of the composition is at least about 10% higher, at least about 15% higher, at least about 20% higher, at least 25% higher, or at least 30% higher as compared to administration of a dose comprising a composition comprising glycopyrronium and formoterol fumarate but no budesonide.

[0115] In some embodiments, method of treatment reduces the mortality of a subject suffering from COPD and cardiovascular disease. In some embodiments the mortality of the subject is reduced by at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, or at least about 70%. In some embodiments, the reduction in mortality refers to the reduction in all-cause mortality.

[0116] In some embodiments, method of treatment reduces the mortality of a subject suffering from cardiovascular disease. In some embodiments, the mortality of the subject is reduced by at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, or at least about 70% compared to the mortality of the subject receiving the GFF treatment. In some embodiments, the reduction in mortality refers to the reduction in all-cause mortality.

[0117] In some embodiments, the method of the disclosure provides a hazard ratio less than about 0.9 for severe COPD exacerbation events as compared to administration of a composition comprising a same dose of glycopyrronium and formoterol fumarate but no budesonide. The term hazard ratio measures the likelihood of an event, e.g., a primary or secondary endpoint as defined herein, in one group (BGF) relative to another group (GFF). In some embodiments, the method provides a hazard ratio less than about 0.7 for severe COPD exacerbation events as compared to administration of a composition comprising a same dose of glycopyrronium and formoterol fumarate but no budesonide. In some embodiments, the method provides a hazard ratio less than about 0.9 for severe cardiac events as compared to administration of a composition comprising a same dose of glycopyrronium and formoterol fumarate but no budesonide but no budesonide. In some embodiments, the method provides a hazard ratio less than about 0.7 for

severe cardiac events as compared to administration of a composition comprising a same dose of glycopyrronium and formoterol fumarate v but no budesonide.

Examples

Example 1: Budesonide, Glycopyrronium and Formoterol Fumarate (BGF) fixed dose combination therapy vs. Glycopyrronium and Formoterol Fumarate (GFF) fixed dose combination therapy

[0118] A randomized, double-blind, parallel group, study is performed, comparing triple therapy composition comprising budesonide, glycopyrronium and formoterol fumarate (BGF) (320/14.4/9.6 µg BID) administered via a metered dose inhaler, or (ii) a double therapy composition (GFF) comprising glycopyrronium and formoterol fumarate (but no budesonide) (14.4/9.6 µg BID) via a metered dose inhaler in participants with COPD who are not receiving ICS and are at risk of a cardiopulmonary event.

[0119] The study consists of 3 periods: a 2-week screening period with run-in using GFF 14.4/9.6 µg BID, a double-blind treatment period for up to 3 years (with a minimum of 3 months), and a follow-up period of 4 weeks after the last dose of study intervention for a total study participation of up to 37 months. Vital status for all participants are assessed at a Study Closeout Visit once it is predicted that 632 primary events that contribute to the primary endpoint have occurred. Participants must not have received maintenance ICS in the prior 12 months and must have a post-bronchodilator FEV1/FVC of < 70% predicted, CAT score ≥ 10, a baseline peripheral blood eosinophil count of > 100 cells/mm³, and a high CV risk. Investigators must ensure all participants with CV risk factors identified during screening (e.g., smoking, high cholesterol, diabetes mellitus, high BP) are managed per national/international standards. After meeting all eligibility criteria at Visit 1, participants initiate run-in with GFF MDI 14.4/9.6 µg taken BID until the evening prior to Visit 2 (randomization) when GFF MDI is discontinued.

[0120] At Visit 2, eligible participants are randomized 1:1 to BGF MDI 320/14.4/9.6 µg or GFF MDI 14.4/9.6 µg for an estimated duration of up to 3 years (with a minimum of 3 months). Following randomization, participants undergo up to 9 additional treatment visits, either at the study site or virtually. Visit 1, Visit 2 (randomization), and Visit 4 are conducted in person at the

study site. All other visits including the Study Closeout Visit may be completed virtually as per participant and investigator preference and/or local regulations and requirements.

[0121] The study is event-driven with each participant expected to be followed for up to 3 years for efficacy and safety endpoints or until 632 participants have at least one primary severe cardiopulmonary event that informs the primary endpoint, if earlier. When the required events have been/are predicted to have been reached, all randomized participants must be scheduled for a Study Closeout Visit to assess primary and secondary objectives (those participants randomized within 3 years of the Study Closeout Visit) and for vital status (all participants). All randomized participants are followed from randomization until study completion, the Study Closeout Visit, or death, whichever comes first, regardless of discontinuation of study intervention, change in respiratory or CV therapy, or occurrence of a non-fatal severe cardiopulmonary event in the endpoint.

CLAIMS

1. A method of treating chronic obstructive pulmonary disease (COPD) in a subject, comprising administering to the subject twice daily a therapeutically effective dose comprising a composition comprising budesonide, glycopyrronium and formoterol fumarate, wherein the dose is administered to the subject via a metered dose inhaler, wherein the subject is at an elevated risk of a COPD exacerbation event and cardiovascular disease.
2. The method of claim 1, wherein the method:
 - (i) reduces risk of a severe COPD event by at least about 10%,
 - (ii) reduces risk of a severe cardiac event by at least about 10%, or
 - (iii) reduces risk of a severe COPD event by at least about 10% and reduces risk of a severe cardiac event by at least about 10%;as compared to administration of a composition comprising a same dose of glycopyrronium and formoterol fumarate but no budesonide.
3. The method of claim 1 or 2, wherein the method reduces risk of a severe COPD event by at least about 15% as compared to administration of a dose comprising a composition comprising glycopyrronium and formoterol fumarate but no budesonide.
4. The method of any one of claims 1 to 3, wherein the method reduces risk of a severe COPD event by at least about 20% as compared to administration of a dose comprising a composition comprising glycopyrronium and formoterol fumarate but no budesonide.
5. The method of any one of claims 1 to 4, wherein the method reduces risk of a severe COPD event by at least about 30% as compared to administration of a dose comprising a composition comprising glycopyrronium and formoterol fumarate but no budesonide.
6. The method of any one of claims 1 to 5, wherein the method reduces risk of a severe COPD event by at least about 40% as compared to administration of a dose comprising a composition comprising glycopyrronium and formoterol fumarate but no budesonide.

7. The method of any one of claims 1 to 6, wherein the method reduces risk of a severe cardiac event by at least about 15% as compared to administration of a dose comprising a composition comprising glycopyrronium and formoterol fumarate but no budesonide.
8. The method of any one of claims 1 to 7, wherein the method reduces risk of a severe cardiac event by at least about 20% as compared to administration of a dose comprising a composition comprising glycopyrronium and formoterol fumarate but no budesonide.
9. The method of any one of claims 1 to 8, wherein the method reduces risk of a severe cardiac event by at least about 30% as compared to administration of a dose comprising a composition comprising glycopyrronium and formoterol fumarate but no budesonide.
10. The method of any one of claims 1 to 9, wherein the method reduces risk of a severe cardiac event by at least about 40% as compared to administration of a dose comprising a composition comprising glycopyrronium and formoterol fumarate but no budesonide.
11. The method of any one of claims 1 to 10, wherein the method:
 - (i) reduces the risk of heart failure (HF) acute healthcare visit/hospitalization,
 - (ii) reduces the risk of myocardial infarction (MI) hospitalization,
 - (iii) reduces the risk of severe COPD exacerbation, and/or
 - (iv) reduces the risk of cardiopulmonary death,relative to subjects being administered a composition comprising a same dose of glycopyrronium and formoterol fumarate but no budesonide.
12. The method of claim 11, wherein the method reduces the risk of heart failure (HF) acute healthcare visit/hospitalization by at least 10%.
13. The method of claim 11, wherein the method reduces the risk of heart failure (HF) acute healthcare visit/hospitalization by at least 20%.
14. The method of claim 11, wherein the method reduces the risk of myocardial infarction (MI) hospitalization by at least 10%.
15. The method of claim 11, wherein the method reduces the risk of myocardial infarction (MI) hospitalization by at least 20%.

16. The method of claim 11, wherein the method reduces the risk of severe COPD exacerbation by at least 10%.
17. The method of claim 11, wherein the method reduces the risk of severe COPD exacerbation by at least 20%.
18. The method of claim 11, wherein the method reduces the risk of cardiopulmonary death by at least 10%.
19. The method of claim 11, wherein the method reduces the risk of cardiopulmonary death by at least 20%.
20. The method of any one of claims 1 to 19, wherein the subject's forced expiratory volume in 1 second area under the curve from 0-6 hours ($FEV_1 AUC_{0-6}$) at 12 weeks following administration of the composition is greater than 110 mL.
21. The method of any one of claims 1 to 20, wherein the subject's $FEV_1 AUC_{0-6}$ at 12 weeks following administration of the composition is at least 10% higher as compared to administration of a dose comprising a composition comprising glycopyrronium and formoterol fumarate but no budesonide.
22. The method of any one of claims 1 to 21, wherein the subject's trough FEV_1 at 12 weeks following administration of the composition is greater than 90 mL.
23. The method of any one of claims 1 to 22, wherein the subject's trough FEV_1 at 12 weeks following administration of the composition is at least 10% higher as compared to administration of a dose comprising a composition comprising glycopyrronium and formoterol fumarate but no budesonide.
24. The method of any one of claims 1 to 23, wherein the dose administered comprises about 220 to about 420 μg budesonide.
25. The method of claim 24, wherein the dose administered comprises about 270 to about 370 μg budesonide.

26. The method of claim 24, wherein the dose administered comprises about 300 to about 340 µg budesonide.
27. The method of any one of claims 24, wherein the dose administered comprises about 320 µg budesonide.
28. The method of any one of claims 1 to 27, wherein the dose administered comprises about 5 to about 35 µg glycopyrronium,
29. The method of claim 28, wherein the dose administered comprises about 10 to about 25 µg glycopyrronium.
30. The method of claim 28, wherein the dose administered comprises about 15 to about 20 µg glycopyrronium.
31. The method of claim 28, wherein the dose administered comprises about 18 µg glycopyrronium.
32. The method of any one of claims 1 to 31, wherein the dose administered comprises about 2 to 20 µg formoterol fumarate.
33. The method of claim 32, wherein the dose administered comprises about 5 to about 15 µg formoterol fumarate.
34. The method of claim 32, wherein the dose administered comprises about 8 to about 12 µg formoterol fumarate.
35. The method of claim 32, wherein the dose administered comprises about 10 µg formoterol fumarate.
36. The method of any one of claims 1 to 35, wherein the dose administered comprises about 300 to about 340 µg budesonide, about 15 to about 20 µg glycopyrronium, and about 8 to about 12 µg formoterol fumarate.

37. The method of claim 36, wherein the dose administered comprises about 320 µg budesonide, about 18 µg glycopyrronium, and about 9 µg to about 10 µg formoterol fumarate are delivered.
38. The method of any one of claims 1 to 37, wherein the dose comprises delivering two metered doses from the metered dose inhaler,
39. The method of claim 38, wherein each metered dose of the two metered doses comprises about 100 to 200 µg budesonide.
40. The method of claim 39, wherein each metered dose of the two metered doses comprises about 2 to about 20 µg glycopyrronium.
41. The method of claim 40, wherein each metered dose of the two metered doses comprises about 1 to about 10 µg formoterol fumarate.
42. The method of claim 39, wherein each metered dose of the two metered doses comprises about 140 to 180 µg budesonide, about 5 to about 15 µg glycopyrronium and about 3 to about 8 µg formoterol fumarate.
43. The method of claim 42, wherein each metered dose of the two metered doses comprises about 160 µg budesonide, about 9 µg glycopyrronium and about 5 µg formoterol fumarate.
44. The method of any one of claims 1 to 43, wherein the composition comprises budesonide and glycopyrronium at a ratio of about 15:1 to about 20:1 (wt/wt).
45. The method of any one of claims 1 to 44, wherein the composition comprises budesonide and glycopyrronium at a ratio of about 16:1 to about 19:1 (wt/wt).
46. The method of any one of claims 1 to 45, wherein the composition comprises budesonide and formoterol at a ratio of about 30:1 to about 40:1 (wt/wt).
47. The method of any one of claims 1 to 46, wherein the composition comprises budesonide and formoterol at a ratio of about 32:1 to about 35:1 (wt/wt).

48. The method of any one of claims 1 to 49, wherein the budesonide, glycopyrronium and formoterol fumarate are in the form of particles, wherein at least 90% of the particles by volume comprise an optical diameter of about 1 μm to about 7 μm .

49. The method of any one of claims 1 to 48, wherein the method provides a hazard ratio less than about 0.9 for severe COPD exacerbation events as compared to administration of a composition comprising a same dose of glycopyrronium and formoterol fumarate but no budesonide.

50. The method of any one of claims 1 to 49, wherein the method provides a hazard ratio less than about 0.7 for severe COPD exacerbation events as compared to administration of a composition comprising a same dose of glycopyrronium and formoterol fumarate but no budesonide.

51. The method of any one of claims 1 to 50, wherein the method provides a hazard ratio less than about 0.9 for severe cardiac events as compared to administration of a composition comprising a same dose of glycopyrronium and formoterol fumarate but no budesonide but no budesonide.

52. The method of any one of claims 1 to 51, wherein the method provides a hazard ratio less than about 0.7 for severe cardiac events as compared to administration of a composition comprising a same dose of glycopyrronium and formoterol fumarate v but no budesonide.

53. The method of any one of claims 1 to 52, wherein the method provides an annualized severe COPD exacerbation event rate at least about 15% lower as compared to administration of a composition comprising a same dose of glycopyrronium and formoterol fumarate but no budesonide.

54. The method of any one of claims 1 to 53, wherein the method provides an annualized severe COPD exacerbation event rate at least about 25% lower as compared to administration of a composition comprising a same dose of glycopyrronium and formoterol fumarate but no budesonide.

55. The method of any one of claims 1 to 54, wherein the method provides an annualized severe cardiac event rate at least about 15% lower as compared to administration of a composition comprising a same dose of glycopyrronium and formoterol fumarate but no budesonide.
56. The method of any one of claims 1 to 55, wherein an annualized severe cardiac event rate of the method is at least about 25% lower as compared to administration of a composition comprising a same dose of glycopyrronium and formoterol fumarate but no budesonide.
57. The method of any one of claims 1 to 56, wherein the composition comprises micronized particles of budesonide.
58. The method of any one of claims 1 to 57, wherein the composition comprises micronized particles of glycopyrronium.
59. The method of any one of claims 1 to 58, wherein the composition comprises micronized particles of formoterol fumarate.
60. The method of any one of claims 1 to 59, wherein the composition comprises a plurality of budesonide particles, a plurality of glycopyrronium particles, a plurality of formoterol fumarate particles, a plurality of respirable suspending particles, and a suspension medium, wherein the plurality of budesonide particles, the plurality of glycopyrronium particles, the plurality of formoterol fumarate particles and the plurality of suspending particles are co-suspended in the suspension medium to form a co-suspension.
61. The method of claim 60, wherein the suspension medium is a pharmaceutically acceptable propellant selected from a hydrofluoroalkane (HFA) propellant, a hydrofluoroolefins (HFO) propellant, a hydrofluorocarbon propellant (HFC), and combination thereof.
62. The method of claim 60 or 61, wherein the suspension medium is a propellant of pharmaceutical grade (1E)-1,3,3,3-Tetrafluoro-1-propene (HFO-1234ze(E)).
63. The method of any one of claims 60 to 62, wherein the respirable suspending particles comprise a volume median optical diameter of about 0.2 μm to about 50 μm .

64. The method of any one of claims 60 to 63, wherein the respirable suspending particles are about 1 mg/mL to about 30 mg/mL in the suspension medium.
65. The method of any one of claims 60 to 64, wherein the respirable suspending particles comprise a phospholipid.
66. The method of claim 65, wherein the phospholipid is 1,2-Distearoyl-sn-glycero-3-phosphocholine (DSPC).
67. The method of any one of claims 60 to 66, wherein a weight ratio of total mass of the respirable suspending particles to total mass of the budesonide, glycopyrronium and formoterol fumarate particles is about 1.5:1 to about 200:1.
68. The method of any one of claims 1 to 67, wherein the subject is not administered greater than 8 metered doses in a 24 hour period.
69. A method of decreasing the mortality of a subject suffering from COPD and cardiovascular disease, the method comprising administering to the subject twice daily a therapeutically effective dose comprising a composition comprising budesonide, glycopyrronium and formoterol fumarate, wherein the dose is administered to the subject via a metered dose inhaler.
70. The method of claim 69, wherein the mortality is all-cause mortality.
71. The method of claim 70, wherein the all-cause mortality of the subject is reduced by at least about 20%.
72. The method of claim 70, wherein the all-cause mortality of the subject is reduced by at least about 30%.
73. The method of claim 70, wherein the all-cause mortality of the subject is reduced by at least about 40%.

74. The method of claim 70, wherein the all-cause mortality of the subject is reduced by at least about 10% compared to a method comprising administering a composition comprising glycopyrronium and formoterol fumarate without budesonide.
75. A method of decreasing the mortality of a subject suffering from cardiovascular disease, the method comprising administering to the subject twice daily a therapeutically effective dose comprising a composition comprising budesonide, glycopyrronium and formoterol fumarate, wherein the dose is administered to the subject via a metered dose inhaler.
76. The method of claim 75, wherein the mortality is all-cause mortality.
77. The method of claim 76, wherein the all-cause mortality of the subject is reduced by at least about 20%.
78. The method of claim 76, wherein the all-cause mortality of the subject is reduced by at least about 30%.
79. The method of claim 76, wherein the all-cause mortality of the subject is reduced by at least about 40%.
80. The method of claim 76, wherein the all-cause mortality of the subject is reduced by at least about 10% compared to a method comprising administering a composition comprising glycopyrronium and formoterol fumarate but no budesonide.
81. A method of reducing the risk of a cardiac event in a subject having cardiovascular disease, the method comprising administering to the subject twice daily a therapeutically effective dose comprising a composition comprising budesonide, glycopyrronium and formoterol fumarate, wherein the dose is administered to the subject via a metered dose inhaler, wherein the subject is at an elevated risk of a COPD exacerbation event and cardiovascular disease.