CLAIMS

1. A method for treating a pulmonary disease or disorder in a patient, the method comprising:

providing a pharmaceutically acceptable co-suspension, the co-suspension comprising:

a suspension medium comprising a pharmaceutically acceptable propellant;

two or more active agents;

one or more species of respirable active agent particles; and

one or more species of respirable suspending particles, wherein the active agent particles and suspending particles associate to form a co-suspension within the suspension medium; and

administering the co-suspension to the patient as a respirable aerosol, wherein said administering of the co-suspension comprises delivering a therapeutically effective amount of the two or more active agents to the patient.

2. The method of claim 1, wherein providing a pharmaceutically acceptable co-suspension comprises providing a co-suspension comprising two or more active agents selected from short-acting beta agonist, long-acting and ultra long-acting β_2 adrenergic receptor agonist (LABA), corticosteroid, anti-inflammatory, anti-tussive, bronchodilator, muscarinic antagonist, and long-acting muscarinic antagonist (LAMA) active agents, including any pharmaceutically acceptable salts, esters, isomers or solvates thereof.

3. The method of claim 2, wherein the pulmonary disease or disorder is selected from at least one of asthma, COPD, chronic bronchitis, emphysema, bronchiectasis, allergic rhinitis, sinusitis, pulmonary vasoconstriction, inflammation, allergies, impeded respiration, respiratory distress syndrome, pulmonary hypertension, pulmonary vasoconstriction, pulmonary inflammation associated with cystic fibrosis, and pulmonary obstruction associated with cystic fibrosis.

4. The method of claim 3, wherein providing a pharmaceutically acceptable co-suspension comprises providing a co-suspension wherein at least one of the at least one species of suspending particles comprises an active agent and the two or more active agents are selected from a LAMA active agent selected from glycopyrrolate, dexipirronium, tiotropium, trospium, aclidinium, and darotropium, a

LABA active agent selected from bambuterol, clenbuterol, formoterol, salmeterol, carmoterol, milveterol, indacaterol, and saligenin- or indole- containing and adamantyl-derived β_2 agonists, and a corticosteroid active agent selected from beclomethasone, budesonide, ciclesonide, flunisolide, fluticasone, methyl-prednisolone, mometasone, prednisone and trimacinolone, including any pharmaceutically acceptable salts, esters, isomers or solvates thereof.

5. The method of claim 3, wherein providing a pharmaceutically acceptable co-suspension comprises providing a co-suspension comprising at least two different species of active agent particles, each of the at least two species of active agent particles comprises a different active agent, and the different active agents are selected from a LAMA active agent selected from glycopyrrolate, dexipirronium, tiotropium, trospium, aclidinium, and darotropium, a LABA active agent selected from bambuterol, clenbuterol, formoterol, salmeterol, carmoterol, milveterol, indacaterol, and saligenin- or indole- containing and adamantyl-derived β_2 agonists, and a corticosteroid active agent selected from beclomethasone, budesonide, ciclesonide, flunisolide, fluticasone, methyl-prednisolone, mometasone, prednisone and trimacinolone, including any pharmaceutically acceptable salts, esters, isomers or solvates thereof.

6. The method of claim 5, wherein providing a pharmaceutically acceptable co-suspension comprises providing a co-suspension comprising at least three different species of active agent particles, each of the at least three species of active agent particles comprises a different active agent, and the different active agents are selected from a LAMA active agent selected from glycopyrrolate, dexipirronium, tiotropium, trospium, aclidinium, and darotropium, a LABA active agent selected from bambuterol, clenbuterol, formoterol, salmeterol, carmoterol, milveterol, indacaterol, and saligenin- or indole- containing and adamantyl-derived β_2 agonists, and a corticosteroid active agent selected from beclomethasone, budesonide, ciclesonide, flunisolide, fluticasone, methyl-prednisolone, mometasone, prednisone and trimacinolone, including any pharmaceutically acceptable salts, esters, isomers or solvates thereof.

7. The method of claim 3, wherein providing a pharmaceutically acceptable co-suspension comprises providing a co-suspension comprising at least two different species of active agent particles, each of the at least two species of active agent particles comprises a different active agent, at least one of the at least

one species of suspending particles comprises a third active agent, and the different active agents are selected from a LAMA active agent selected from glycopyrrolate, dexipirronium, tiotropium, trospium, aclidinium, and darotropium, a LABA active agent selected from bambuterol, clenbuterol, formoterol, salmeterol, carmoterol, milveterol, indacaterol, and saligenin- or indole- containing and adamantyl-derived β_2 agonists, and a corticosteroid active agent selected from beclomethasone, budesonide, ciclesonide, flunisolide, fluticasone, methyl-prednisolone, mometasone, prednisone and trimacinolone, including any pharmaceutically acceptable salts, esters, isomers or solvates thereof.

8. The method of claim 3, wherein delivering a therapeutically effective amount of the two or more active agents to the patient comprises simultaneously delivering therapeutically effective amounts of a LAMA active agent selected from glycopyrrolate, dexipirronium, tiotropium, trospium, aclidinium, and darotropium, and a LABA active agent selected from bambuterol, clenbuterol, formoterol, salmeterol, carmoterol, milveterol, indacaterol, and saligenin- or indole- containing and adamantyl-derived β_2 agonists, including any pharmaceutically acceptable salts, esters, isomers or solvates thereof.

9. The method of claim 3, wherein delivering a therapeutically effective amount of the two or more active agents to the patient comprises simultaneously delivering therapeutically effective amounts of a LAMA active agent selected from glycopyrrolate, dexipirronium, tiotropium, trospium, aclidinium, and darotropium, and a corticosteroid active agent selected from beclomethasone, budesonide, ciclesonide, flunisolide, fluticasone, methyl-prednisolone, mometasone, prednisone and trimacinolone, including any pharmaceutically acceptable salts, esters, isomers or solvates thereof.

10. The method of claim 3, wherein delivering a therapeutically effective amount of the two or more active agents to the patient comprises simultaneously delivering therapeutically effective amounts of a LABA active agent selected from bambuterol, clenbuterol, formoterol, salmeterol, carmoterol, milveterol, indacaterol, and saligenin- or indole- containing and adamantyl-derived β_2 agonists, and a corticosteroid active agent selected from beclomethasone, budesonide, ciclesonide, flunisolide, fluticasone, methyl-prednisolone, mometasone, prednisone and trimacinolone, including any pharmaceutically acceptable salts, esters, isomers or solvates thereof.

11. The method of claim 3, wherein delivering a therapeutically effective amount of the two or more active agents to the patient comprises simultaneously delivering therapeutically effective amounts of a LAMA active agent selected from glycopyrrolate, dexipirronium, tiotropium, trospium, aclidinium, and darotropium, a LABA active agent selected from bambuterol, clenbuterol, formoterol, salmeterol, carmoterol, milveterol, indacaterol, and saligenin- or indole- containing and adamantyl-derived β_2 agonists, and a corticosteroid active agent selected from beclomethasone, budesonide, ciclesonide, flunisolide, fluticasone, methyl-prednisolone, mometasone, prednisone and trimacinolone, including any pharmaceutically acceptable salts, esters, isomers or solvates thereof.

12. A method according to any of claims 1 through 11, wherein administering the co-suspension to the patient results in a clinically significant increase in FEV_1 in the patient.

13. The method of claim 12, wherein administering the co-suspension to the patient results in an increase in FEV_1 of at least 150 mL within a period of time selected from 0.5 hours or less, 1 hour or less, and 1.5 hours or less.

14. The method of claim 13, wherein administering the co-suspension to the patient results in an increase in FEV_1 of at least 200 mL within a period of time selected from 0.5 hours or less, 1 hour or less, and 1.5 hours or less.

15. The method of claim 14, wherein administering the co-suspension to the patient results in an increase in FEV_1 of at least 250 mL within a period of time selected from 0.5 hours or less, 1 hour or less, and 1.5 hours or less.

16. The method of claim 15, wherein administering the co-suspension to the patient results in an increase in FEV_1 of at least 300 mL within a period of time selected from 0.5 hours or less, 1 hour or less, and 1.5 hours or less.

17. The method of claim 16, wherein administering the co-suspension to the patient results in an increase in FEV_1 of at least 350 mL within a period of time selected from 0.5 hours or less, 1 hour or less, and 1.5 hours or less.

18. A method according to any of claims 1 through 17, wherein the clinically significant increase in FEV_1 achieved by administering the co-suspension to the patient remains clinically significant for a period of time selected from up to 4 hours, up to 6 hours, up to 8 hours, up to 10 hours, and up to 12 hours, or more.

19. A method according to any of claims 1 through 17, wherein administering the co-suspension to the patient results in a 10% or greater increase in

FEV_1 within a period of time selected from 0.5 hours or less, 1 hour or less, 1.5 hours or less, and 2 hours in 50% or more of patients.

20. A method according to any of claims 1 through 17, wherein administering the co-suspension to the patient results in a 10% or greater increase in FEV_1 within a period of time selected from 0.5 hours or less, 1 hour or less, 1.5 hours or less, and 2 hours in 60% or more of patients.

21. A method according to any of claims 1 through 17, wherein administering the co-suspension to the patient results in a 10% or greater increase in FEV_1 within a period of time selected from 0.5 hours or less, 1 hour or less, 1.5 hours or less, and 2 hours in 70% or more of patients.

22. A method according to any of claims 1 through 17, wherein administering the co-suspension to the patient results in a 10% or greater increase in FEV_1 within a period of time selected from 0.5 hours or less, 1 hour or less, 1.5 hours or less, and 2 hours in 80% or more of patients.

23. A method according to any of claims 1 through 11, wherein administering the co-suspension to the patient results in patients experiencing either an increase from baseline in FEV_1 of at least 200 ml or a 12%, or greater, increase from baseline in FEV_1 coupled with total increase in FEV_1 of at least 150 ml.

24. A method according to any of claims 1 through 11, wherein administering the co-suspension to the patient results in patients experiencing either an increase from baseline in FEV_1 of at least 200 ml or a 12%, or greater, increase from baseline in FEV_1 coupled with total increase in FEV_1 of at least 150 ml within a period of time selected from 1 hour, or less, 1.5 hours or less, 2 hours, or less, and 2.5 hours, or less.

25. The method of claim 24, wherein either the increase from baseline in FEV_1 of at least 200 ml or the 12%, or greater, increase from baseline in FEV_1 coupled with total increase in FEV_1 of at least 150 ml is experienced in at least 50% of patients within a period of time selected from 1 hour, or less, 1.5 hours or less, 2 hours, or less, and 2.5 hours, or less.

26. The method of claim 25, wherein either the increase from baseline in FEV_1 of at least 200 ml or the 12%, or greater, increase from baseline in FEV_1 coupled with total increase in FEV_1 of at least 150 ml is experienced in at least 60% of patients within a period of time selected from 1 hour, or less, 1.5 hours or less, 2 hours, or less, and 2.5 hours, or less.

27. The method of claim 24, wherein either the increase from baseline in FEV_1 of at least 200 ml or the 12%, or greater, increase from baseline in FEV_1 coupled with total increase in FEV_1 of at least 150 ml is experienced in at least 70% of patients within a period of time selected from 1 hour, or less, 1.5 hours or less, 2 hours, or less, and 2.5 hours, or less.

28. The method of claim 24, wherein either the increase from baseline in FEV_1 of at least 200 ml or the 12%, or greater, increase from baseline in FEV_1 coupled with total increase in FEV_1 of at least 150 ml is experienced in at least 80% of patients within a period of time selected from 1 hour, or less, 1.5 hours or less, 2 hours, or less, and 2.5 hours, or less.

29. A method according to any of claims 1 through 28, wherein administering the co-suspension to the patient results in a clinically significant increase in FEV_1 in the patient and the clinically significant increase in FEV_1 is a significant improvement over the increase provided by a composition delivering only one of the two or more active agents.

30. The method of claim 29, wherein the significant improvement in FEV_1 is 70 ml or greater.

31. The method of claim 30, wherein the significant improvement in FEV_1 is 80 ml or greater.

32. The method of claim 31, wherein the significant improvement in FEV_1 is 90 ml or greater.

33. A method according to any of claims 30 through 32, wherein the significant improvement is measured as an improvement in peak FEV_1.

34. A method according to any of claims 30 through 32, wherein the significant improvement is measured as an improvement in FEV_1 AUC_{0-12}.

35. A method according to any of claims 1 through 34, wherein administering the co-suspension to the patient results in a clinically significant increase in inspiratory capacity (IC).

36. A method according to claim 35, wherein the clinically significant increase in IC is an increase of 100 ml or greater.

37. A method according to claim 36, wherein the clinically significant increase in IC is an increase of 200 ml or greater.

38. A method according to claim 37, wherein the clinically significant increase in IC is an increase of 300 ml or greater.

39. A method according to claim 38, wherein the clinically significant increase in IC is an increase of 350 ml or greater.

40. A method according to any of claims 35 through 39, wherein the clinically significant increase in IC is achieved in 2 hours or less.

41. A method according to any of claims 35 through 40, wherein the clinically significant increase in IC is achieved in 1 hour or less.

42. A method according to any preceding claim, wherein the suspension medium included in the co-suspension provided and administered as a respirable aerosol comprises a propellant selected from an HFA propellant, a PFC propellant and combinations thereof, and the propellant is substantially free of additional constituents.

43. A method according to any preceding claim, wherein the suspension medium included in the co-suspension provided and administered as a respirable aerosol consists essentially of a propellant selected from an HFA propellant, a PFC propellant and combinations thereof, and the propellant is substantially free of additional constituents.

44. A method according to any preceding claim, wherein the two or more active agents included in the co-suspension provided and administered as a respirable aerosol are selected from a LAMA active agent selected from glycopyrrolate, dexipirronium, tiotropium, trospium, aclidinium, and darotropium, including any pharmaceutically acceptable salts, esters, isomers or solvates thereof, and a LABA active agent selected from bambuterol, clenbuterol, formoterol, salmeterol, carmoterol, milveterol, indacaterol, and saligenin- or indole- containing and adamantyl-derived β_2 agonists, including any pharmaceutically acceptable salts, esters, isomers or solvates thereof, and the respirable suspending particles included in the co-suspension provided and administered as a respirable aerosol comprise an excipient selected from at least one of lipids, phospholipids, nonionic detergents, polymers, nonionic block copolymers, surfactants, non-ionic surfactants, biocompatible fluorinated surfactants, carbohydrates, and combinations thereof.

45. The method of claim 44, wherein the respirable suspending particles comprise perforated microstructures.

46. A method according to either of claims 44 and 45, wherein the respirable suspending particles comprise DSPC and calcium chloride.

47. A method according to any of claims 42 through 46, wherein at least 50% by volume of the active agent particles included in the co-suspension provided and administered as a respirable aerosol exhibit an optical diameter of 5 μm or less.

48. A method according to any preceding claim, wherein the respirable suspending particles included in the co-suspension provided and administered as a respirable aerosol are included in the suspension medium at a concentration selected from between about 1 mg/ml and about 15 mg/ml, between about 3 mg/ml and about 10 mg/ml, between about 5 mg/ml and about 8 mg/ml, and about 6 mg/ml.

49. A method according to any preceding claim, wherein the respirable suspending particles included in the co-suspension provided and administered as a respirable aerosol exhibit an MMAD selected from between about 10 μm and about 500 nm, between about 5 μm and about 750 nm, between about and 1 μm and about 3 μm.

50. A method according to any preceding claim, wherein the respirable suspending particles included in the co-suspension provided and administered as a respirable aerosol exhibit a volume median optical diameter selected from between about 0.2 μm and about 50 μm, between about 0.5 μm and about 15 μm, between about 1.5 μm and about 10 μm, and between about 2 μm and about 5 μm.

51. A method according to any preceding claim, wherein a ratio of the total mass of the respirable suspending particles to the total mass of at least one species of agent particles is selected from above about 1.5, up to about 5, up to about 10, up to about 15, up to about 17, up to about 20, up to about 30, up to about 40, up to about 50, up to about 60, up to about 75, up to about 100, up to about 150, and up to about 200.

52. A method according to any preceding claim, wherein a ratio of the total mass of the at least one species of suspending particles to the total mass of the at least one species of active agent particles is selected from between about 3:1 and about 15:1 and between about 2:1 and 8:1.

53. A method according to any preceding claim, wherein the respirable suspending particles included in the co-suspension provided and administered as a respirable aerosol remain associated with the active agent particles even when subjected to buoyancy forces amplified by centrifugation at an acceleration selected from accelerations of at least 1 g, at least 10 g, at least 50 g, and at least 100 g.

54. A method according to any preceding claim, wherein the active agent particles included in the co-suspension provided and administered as a respirable aerosol comprise a first species and a second species of active agent particles, with the first species of active agent particles comprising glycopyrrolate, including any pharmaceutically acceptable salts, esters, isomers or solvates thereof, and the second species of active agent particles comprising formoterol, including any pharmaceutically acceptable salts, esters, isomers or solvates thereof.

55. The method of claim 54, wherein the first species of active agent particles comprise crystalline glycopyrrolate and the second species of active agent particles comprise crystalline formoterol.

56. The method of claim 54, wherein the co-suspension provided and administered as a respirable aerosol consists essentially of an HFA propellant substantially free of additional constituents, two active agents provided as first and second species of active agent particles, and respirable suspending particles formed from a phospholipid excipient, wherein the two active agents are provided as first and second species of active agent particles, the first species of active agent particles comprise crystalline glycopyrrolate, including any pharmaceutically acceptable salts, esters, isomers or solvates thereof, and the second species of active agent particles comprise formoterol, including any pharmaceutically acceptable salts, esters, isomers or solvates thereof.

57. A method according to any preceding claim, wherein the pharmaceutically acceptable co-suspension is provided in and administered from an MDI.

58. A method according to any of claims 44 through 57, wherein administering the co-suspension to the patient as a respirable aerosol comprises administering the co-suspension to the patient up to two times daily, and each administration comprises delivering no more than 150 µg of the LAMA active agent and no more than 12 µg of the LABA active agent.

59. A method according to any of claims 44 through 58, wherein administering the co-suspension to the patient as a respirable aerosol comprises administering the co-suspension to the patient up to two times daily, and each administration comprises delivering no more than 100 µg of the LAMA active agent and no more than 12 µg of the LABA active agent.

60. A method according to any of claims 44 through 59, wherein administering the co-suspension to the patient as a respirable aerosol comprises administering the co-suspension to the patient up to two times daily, and each administration comprises delivering no more than 80 µg of the LAMA active agent and no more than 12 µg of the LABA active agent.

61. A method according to any of claims 44 through 60, wherein administering the co-suspension to the patient as a respirable aerosol comprises administering the co-suspension to the patient up to two times daily, and each administration comprises delivering no more than 50 µg of the LAMA active agent and no more than 12 µg of the LABA active agent.

CLAIMS

1. Use of a pharmaceutically acceptable co-suspension in the manufacture of a medicament for use in the treatment of a pulmonary disease or disorder by administration of the co-suspension to the patient twice daily as a respirable aerosol, wherein said pharmaceutically acceptable co-suspension comprises:

a suspension medium comprising a pharmaceutically acceptable propellant,

a first species of respirable active agent particles comprising glycopyrrolate or a pharmaceutically acceptable salt, ester, isomer or solvate thereof,

a second species of respirable active agent particles comprising formoterol or a pharmaceutically acceptable salt, ester, isomer or solvate thereof,

one or more species of respirable suspending particles, wherein the first and second species of respirable active agent particles and the respirable suspending particles co-locate to form a co-suspension within the suspension medium,

wherein a therapeutically effective amount of the glycopyrrolate or pharmaceutically acceptable salt, ester, isomer or solvate thereof and formoterol or pharmaceutically acceptable salt, ester, isomer or solvate thereof, comprising no more than 150 µg of the glycopyrrolate or pharmaceutically acceptable salt, ester, isomer or solvate thereof and no more than 12 µg of the formoterol or pharmaceutically acceptable salt, ester, isomer or solvate thereof, is delivered to the patient at each administration.

2. The use according to claim 1 wherein no more than 100 µg of the glycopyrrolate or pharmaceutically acceptable salt, ester, isomer or solvate thereof and no more than 12 µg of the formoterol or pharmaceutically acceptable salt, ester, isomer or solvate thereof are to be delivered to the patient at each administration.

3. The use according to claim 1 or 2 wherein no more than 80 µg of the glycopyrrolate or pharmaceutically acceptable salt, ester, isomer or solvate thereof and no more than 12 µg of the formoterol or pharmaceutically acceptable salt, ester, isomer or solvate thereof are to be delivered to the patient at each administration.

4. The use according to any preceding claim wherein no more than 50 µg of the glycopyrrolate or pharmaceutically acceptable salt, ester, isomer or solvate thereof and no more than 12 µg of the formoterol or pharmaceutically acceptable salt, ester, isomer or solvate thereof are to be delivered to the patient at each administration.

5. The use according to claim 1 wherein no more than 72 µg of glycopyrrolate is to be delivered to the patient at each administration.

6. The use according to claim 1 wherein no more than 36 µg of glycopyrrolate is to be delivered to the patient at each administration.

7. The use according to any preceding claim, wherein the co-suspension is suitable for delivery from a metered dose inhaler and wherein;

the suspension medium comprises a pharmaceutically acceptable HFA propellant substantially free of additional materials; and

the respirable suspending particles comprise a phospholipid material that is substantially insoluble in the propellant, wherein the total mass of the respirable suspending particles exceeds the total mass of the first and second species of respirable active agent particles.

8. The use according to any preceding claim, wherein the pulmonary disease or disorder is selected from at least one of the group consisting of asthma, COPD, allergic rhinitis, sinusitis, pulmonary vasoconstriction, inflammation, allergies, impeded respiration, respiratory distress syndrome, pulmonary hypertension, pulmonary inflammation experienced with cystic fibrosis, and pulmonary obstruction experienced with cystic fibrosis.

9. The use according to any preceding claim, wherein the pulmonary disease or disorder is COPD.

10. The use according to any preceding claim, wherein the glycopyrrolate is in any crystalline form.

11. The use according to any preceding claim, wherein the formoterol is in any crystalline form.

12. The use according to any preceding claim wherein the ratio of the total mass of the respirable suspending particles to the total mass of the first and second species of respirable active agent particles is from above 1 and up to 200.

13. The use according to claim 12, wherein the ratio of the total mass of the respirable suspending particles to the total mass of the first and second species of respirable active agent particles is selected from the ranges of between 10 and 200, between 60 and 200, between 15 and 60, and between 15 and 170.

14. The use according to any preceding claim, wherein the co-suspension comprises a pharmaceutically acceptable salt of glycopyrrolate selected from fluoride, chloride, bromide, iodide, nitrate, sulfate, phosphate, formate, acetate, trifluoroacetate, propionate, butyrate, lactate, citrate, tartrate, malate, maleate, succinate, benzoate, p-chlorobenzoate, diphenyl-acetate or triphenylacetate, o-hydroxybenzoate, p-hydroxybenzoate, 1 -hydroxynaphthalene-2-carboxylate, 3-hydroxynaphthalene-2-carboxylate, methanesulfonate, and benzenesulfonate salts.

15. The use according to claim 14, wherein the pharmaceutically acceptable salt of glycopyrrolate is selected from fluoride, chloride, bromide, and iodide salts.

16. The use according to any preceding claim, wherein the pharmaceutically acceptable salt of glycopyrrolate is 3-[(cyclopentyl-hydroxyphenylacetyl)oxy]-1,1 -dimethylpyrrolidinium bromide.

17. The use according to any preceding claim, wherein the co-suspension comprises a pharmaceutically acceptable salt of formoterol selected from hydrochloric, hydrobromic, sulfuric, phosphoric, fumaric, maleic, acetic, lactic, citric, tartaric, ascorbic, succinic, glutaric, gluconic, tricarballylic, oleic, benzoic, p-methoxybenzoic, salicylic, o- and p-hydroxybenzoic, p-chlorobenzoic, methanesulfonic, p-toluenesulfonic and 3-hydroxy-2-naphthalene carboxylic acid salts.

18. The use according to claim 17, wherein the pharmaceutically acceptable salt of formoterol is formoterol fumarate.