# NOVEL DOSAGE AND FORMULATION

**[0001]** This invention relates to a novel dosage for aclidinium and to novel methods and formulations for the treatment of respiratory diseases, especially asthma and chronic obstructive pulmonary disease (COPD), using aclidinium.

## BACKGROUND

**[0002]** Aclidinium bromide is 3(R)-(2-hydroxy-2,2-dithien-2-ylacetoxy)-1-(3-phenoxypropyl)-1-azoniabicyclo[2.2.2]octane bromide, described in, e.g., WO 0104118. Although this compound is known to be a long-acting anticholinergic useful in the treatment of respiratory diseases, the optimal dosage is not disclosed.

## SUMMARY OF THE INVENTION

**[0003]** It is now surprisingly found that, for treatment of respiratory disorders, particularly asthma and COPD, in an adult human, aclidinium is most effective upon administration by inhalation in a dosage of about 400 μg metered nominal dose, typically a single dosage of about 400 micrograms per day metered nominal dose, (e.g., about 360 μg emitted dose, and about 120 μg Fine Particle dose) (weight corresponding to aclidinium bromide).

**[0004]** The invention thus provides in a first embodiment a pharmaceutical composition for inhalation comprising aclidinium in the form of a dry powder of a pharmaceutically acceptable salt, e.g., aclidinium bromide, in admixture with a pharmaceutically acceptable dry powder carrier, e.g., lactose particles, (i) comprising a single metered nominal dose of aclidinium equivalent to about 400 μg aclidinium bromide, or (ii) in a multidose dry powder inhaler device calibrated to provide a metered nominal dose of aclidinium equivalent to about 400 μg aclidinium bromide. This composition can be administered one or more times per day. Preferably once or twice a day.

**[0005]** In a second embodiment, the invention provides a method of treating a respiratory condition, e.g., selected from asthma and chronic obstructive pulmonary disease, in a patient in need of such treatment, comprising administering a dose, typically a single daily dose or twice daily dose, of aclidinium, e.g., aclidinium bromide, equivalent to about 400 μg metered nominal dose aclidinium bromide, e.g., comprising administering a pharmaceutical composition

according to the previous paragraph. The invention further provides the use of aclidinium in the manufacture of a medicament, e.g., as described in the preceding paragraph, for use in such a method.

**[0006]** The aclidinium may be administered as monotherapy, or in combination with one or more additional anti-inflammatory and/or bronchodilating agents, e.g., corticosteroids, PDE IV inhibitors and β2-agonists, e.g., formoterol, salmeterol, budesonide, and mometasone, and the invention thus further provides methods as described above further comprising administration of an effective amount of such an agent, as well as pharmaceutical compositions as described above, further comprising such additional agent(s).

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DETAILED DESCRIPTION OF THE INVENTION

**[0007]** Typically, the aclidinium is administered in the form of a salt with an anion X, wherein X is a pharmaceutically acceptable anion of a mono or polyvalent acid. More typically, X is an anion derived from an inorganic acid, such as hydrochloric acid, hydrobromic acid, sulphuric acid and phosphoric acid, or an organic acid such as methanesulphonic acid, acetic acid, fumaric acid, succinic acid, lactic acid, citric acid or maleic acid. Preferably the aclidinium is in the form of aclidinium bromide.

**[0008]** The aclidinium is preferably administered in the form of a dry powder, in admixture with a suitable carrier, e.g., lactose powder, suitable for inhalation.

20 **[0009]** For example, in one embodiment, the aclidinium is aclidinium bromide in admixture with lactose powder.

**[0010]** The respiratory disease or condition to be treated with the formulations and methods of the present invention is typically asthma, acute or chronic bronchitis, emphysema, chronic obstructive pulmonary disease (COPD), bronchial hyperreactivity or rhinitis, in particular asthma or chronic obstructive pulmonary disease (COPD), especially COPD.

**[0011]** In the context of dosage of an active agent, "about" as used herein means within the normal limits of acceptable variations as defined by the European and US Pharmacopeia of plus/minus 35% or preferably acceptable variations as defined by the current most stringent requirement, the US FDA draft guidance for inhaler of plus/minus 25% or especially within the

30 metered dosing accuracy for the dispensing system e.g. +/- 10% Thus a metered nominal dose of "about 400 μg" is meant a target dose of 400 μg subject to variation within the normal limits of

acceptance for the dispensing system, e.g. plus/minus 35% (acceptable variations as defined by the European and US Pharmacopeia) or preferably 300-500 μg (or acceptable variations as defined by the current most stringent requirement, the US FDA draft guidance for inhaler) or especially 340-460 μg (or within the metered dosing accuracy of the inhaler).

**[0012]** The emitted dose and the fine particle dose (fine particle dose = μg aclidinium bromide in the emitted dose below a cut off aerodynamic threshold of 5 micrometer) are subjected to the same variation and proportional to the metered dose and are therefore for the emitted dose e.g. a metered nominal dose of about 400 μg (plus/minus 35%) corresponds to about 360 μg emitted dose (plus/minus 35%), and about 120 micrograms Fine Particle dose (plus/minus 35%)

**[0013]** Packaging of the formulation may be suitable for unit dose or multi-dose delivery. In the case of multi-dose delivery, the formulation can be pre-metered or metered in use. Dry powder inhalers are thus classified into three groups: (a) single dose, (b) multiple unit dose and (c) multi dose devices.

**[0014]** Formulations generally contain a powder mix for inhalation of the compounds of the invention and a suitable powder base (carrier substance) such as lactose or starch. Use of lactose is preferred. Each capsule or cartridge may generally contain between 2μg and 400 μg of each therapeutically active ingredient. Alternatively, the active ingredient (s) may be presented without excipients.

**[0015]** For single dose inhalers of the first type, single doses have been weighed by the manufacturer into small containers, which are mostly hard gelatine capsules. A capsule has to be taken from a separate box or container and inserted into a receptacle area of the inhaler. Next, the capsule has to be opened or perforated with pins or cutting blades in order to allow part of the inspiratory air stream to pass through the capsule for powder entrainment or to discharge the powder from the capsule through these perforations by means of centrifugal force during inhalation. After inhalation, the emptied capsule has to be removed from the inhaler again. Mostly, disassembling of the inhaler is necessary for inserting and removing the capsule, which is an operation that can be difficult and burdensome for some patients. Other drawbacks related to the use of hard gelatine capsules for inhalation powders are (a) poor protection against moisture uptake from the ambient air, (b) problems with opening or perforation after the capsules have been exposed previously to extreme relative humidity, which causes fragmentation or

indenture, and (c) possible inhalation of capsule fragments. Moreover, for a number of capsule inhalers, incomplete expulsion has been reported.

**[0016]** Some capsule inhalers have a magazine from which individual capsules can be transferred to a receiving chamber, in which perforation and emptying takes place, as described in WO 92/03175. Other capsule inhalers have revolving magazines with capsule chambers that can be brought in line with the air conduit for dose discharge (e. g. WO91/02558 and GB 2242134). They comprise the type of multiple unit dose inhalers together with blister inhalers, which have a limited number of unit doses in supply on a disk or on a strip.

**[0017]** Blister inhalers provide better moisture protection of the medicament than capsule inhalers. Access to the powder is obtained by perforating the cover as well as the blister foil, or by peeling off the cover foil. When a blister strip is used instead of a disk, the number of doses can be increased, but it is inconvenient for the patient to replace an empty strip. Therefore, such devices are often disposable with the incorporated dose system, including the technique used to transport the strip and open the blister pockets.

**[0018]** Multi-dose inhalers do not contain pre-measured quantities of the powder formulation. They consist of a relatively large container and a dose measuring principle that has to be operated by the patient. The container bears multiple doses that are isolated individually from the bulk of powder by volumetric displacement. Various dose measuring principles exist, including rotatable membranes (e. g. EP0069715) or disks (e. g. GB 2041763; EP 0424790; DE 4239402 and EP 0674533), rotatable cylinders (e. g. EP 0166294; GB 2165159 and WO 92/09322) and rotatable frustums (e. g. WO 92/00771), all having cavities which have to be filled with powder from the container. Other multi dose devices have measuring slides (e. g.US 5201308 and WO 97/00703) or measuring plungers with a local or circumferential recess to displace a certain volume of powder from the container to a delivery chamber or an air conduit e. g. EP 0505321, WO 92/04068 and WO 92/04928.

**[0019]** Reproducible dose measuring is one of the major concerns for multi dose inhaler devices. The powder formulation has to exhibit good and stable flow properties, because filling of the dose measuring cups or cavities is mostly under the influence of the force of gravity. For reloaded single dose and multiple unit dose inhalers, the dose measuring accuracy and reproducibility can be guaranteed by the manufacturer. Multi dose inhalers on the other hand,

can contain a much higher number of doses, whereas the number of handlings to prime a dose is generally lower.

**[0020]** Because the inspiratory air stream in multi-dose devices is often straight across the dose measuring cavity, and because the massive and rigid dose measuring systems of multi dose inhalers can not be agitated by this inspiratory air stream, the powder mass is simply entrained from the cavity and little de-agglomeration is obtained during discharge.

**[0021]** Consequently, separate disintegration means are necessary. However in practice, they are not always part of the inhaler design. Because of the high number of doses in multi-dose devices, powder adhesion onto the inner walls of the air conduits and the de- agglomeration means must be minimized and/or regular cleaning of these parts must be possible, without affecting the residual doses in the device. Some multi dose inhalers have disposable drug containers that can be replaced after the prescribed number of doses has been taken (e. g. WO 97/000703). For such semi-permanent multi dose inhalers with disposable drug containers, the requirements to prevent drug accumulation are even stricter.

**[0022]** In a preferred embodiment, the aclidinium is administered via a breath-activated, multidose, dry powder inhaler, calibrated to permit daily dosing of 400 μg metered nominal dose of aclidinium. An especially preferred inhaler device for this purpose is Genuair®, (formerly known as Novolizer SD2FL), or as described in WO 97/000703, WO 03/000325, or WO 03/061742, the contents of which applications are incorporated herein by reference.

**[0023]** Apart from applications through dry powder inhalers the compositions of the invention can be administered in aerosols which operate via propellant gases or by means of so-called atomisers or nebulizers, via which solutions or suspensions of pharmacologically-active substances can be sprayed under high pressure so that a mist of inhalable particles results.

**[0024]** Medicaments for administration by inhalation desirably have a controlled particle size. The optimum particle size for inhalation into the bronchial system is usually 1-10μm, preferably 2-5μm. Particles having a size above 20μ are generally too large when inhaled to reach the small airways. To achieve these particle sizes the particles of the active ingredient as produced may be size reduced by conventional means eg by micronisation or supercritical fluid techniques. The desired fraction may be separated out by air classification or sieving. Preferably, the particles will be crystalline.

**[0025]** Achieving a high dose reproducibility with micronised powders is difficult because of their poor flowability and extreme agglomeration tendency. To improve the efficiency of dry powder compositions, the particles should be large while in the inhaler, but small when discharged into the respiratory tract. Thus, an excipient, for example a mono-, di- or polysaccharide or sugar alcohol, e.g., such as lactose, mannitol or glucose is generally employed. The particle size of the excipient will usually be much greater than the inhaled medicament within the present invention. When the excipient is lactose it will typically be present as lactose particles, preferably crystalline alpha lactose monohydrate, e.g., having an average particle size range of 20-1000 μm, preferably in the range of 90-150 μm. The median particle size approximately corresponds to the average and is the diameter where 50 mass-% of the particles have a larger equivalent diameter, and the other 50 mass-% have a smaller equivalent diameter. Hence the average particle size is generally referred to in the art as equivalent d50. The distribution of particle size around may affect flow properties, bulk density, etc. Hence to characterize a particle size diameter, other equivalent diameters can be used in addition to d50, such as d10 and d90. d10 is the equivalent diameter where 10 mass-% of the particles have a smaller diameter (and hence the remaining 90% is coarser). d90 is the equivalent diameter where 90 mass-% of the particles have a smaller diameter. In one embodiment, the lactose particles for use in formulations of the invention have a d10 of 90 - 160 μm, a d50 of 170 – 270 μm, and d90 of 290 – 400 μm.

**[0026]** Suitable lactose materials for use in the present invention are commercially available, e.g., from DMW Internacional (Respitose GR-001, Respitose SV-001, Respitose SV-003); Meggle (Capsulac 60, Inhalac 70, Capsulac 60 INH); and Borculo Domo (Lactohale 100-200, Lactohale 200-300, and Lactohale 100-300).

**[0027]** The ratio between the lactose particles and the aclidinium by weight will depend on the inhaler device used, but is typically, e.g., 5:1 to 100:1, for example 25:1 to 75:1, e.g., 30-35:1.

**[0028]** In a preferred embodiment, the aclidinium is administered in the form of a dry powder formulation of aclidinium bromide in admixture with lactose, in a ratio by weight of aclidinium to lactose of 1:50 to 1:75, suitable for administration via a dry powder inhaler, wherein the aclidinium particles have an average particle size of from 2 to 5μm in diameter, e.g., less than 3 μm in diameter, and the lactose particles have have a d10 of 90 - 160 μm, a d50 of 170 – 270 μm, and d90 of 290 – 400 μm.

**[0029]** Additional active agents such as β2-agonists , PDE IV inhibitors, corticosteroids, leukotriene D4 antagonists, inhibitors of egfr-kinase, p38 kinase inhibitors or NK1 receptor agonists may be utilized in the methods and formulations of the inventions. For example, the invention provides aclidinium formulations as described herein further comprising an effective amount of one or more such additional active agents, e.g. further comprising an effective amount of a β2-agonist and/or a PDE IV inhibitor and/or a corticosteroid. The invention also provides methods for treating respiratory conditions as herein before described, e.g., asthma or COPD, comprising administering an aclidinium formulation as described herein and further comprising administering simultaneously an effective amount of one or more such additional active agents, e.g. further comprising an effective amount of a β2-agonist and/or a PDE IV inhibitor and/or a corticosteroid.

**[0030]** β2-agonists suitable for use with the aclidinium in the present invention include, e.g., arformoterol, bambuterol, bitolterol, broxaterol, carbuterol, clenbuterol, dopexamine, fenoterol, formoterol, hexoprenaline, ibuterol, isoetharine, isoprenaline, levosalbutamol, mabuterol, meluadrine, metaprotenerol, nolomirole, orciprenaline, pirbuterol, procaterol, reproterol, ritodrine, rimoterol, salbutamol, salmefamol, salmeterol, sibenadet, sotenerot, sulfonterol, terbutaline, tiaramide, tulobuterol, GSK-597901, milveterol, GSK-678007, GSK-642444, GSK-159802, HOKU-81, LAS100977 (5-(2-{[6-(2,2-difluoro-2-phenylethoxy)hexyl]amino}-1*(R)*-hydroxyethyl)-8-hydroxyquinolin-2(1*H*)-one), KUL-1248, carmoterol, indacaterol and 5-[2-(5,6-diethylindan-2-ylamino)-1-hydroxyethyl]-8-hydroxy-1H-quinolin-2-one, 4-hydroxy-7-[2-{[2-{[3-(2-phenylethoxy)propyl]sulfonyl} ethyl]amino}ethyl]-2(3H)-benzothiazolone, 1-(2-fluoro-4-hydroxyphenyl)-2-[4-(1-benzimidazolyl)-2-methyl-2-butylamino]ethanol, 1-[3-(4-methoxybenzylamino)-4-hydroxyphenyl]-2-[4-(1-benzimidazolyl)-2-methyl-2-butylamino]ethanol, 1-[2H-5-hydroxy-3-oxo-4H-1,4-benzoxazin-8-yl]-2-[3-(4-N,N -dimethylaminophenyl)-2-methyl-2-propylamino]ethanol, 1-[2H-5-hydroxy-3-oxo-4H-1,4-benzoxazin-8-yl]-2-[3-(4-methoxyphenyl)-2-methyl-2-propylamino]ethanol, 1-[2H-5-hydroxy-3-oxo-4H-1,4-benzoxazin-8-yl]-2-[3-(4-n-butyloxyphenyl)-2-methyl-2-propylamino]ethanol, 1-[2H-5-hydroxy-3-oxo-4H-1,4-benzoxazin-8-yl]-2-{4-[3-(4-methoxyphenyl)-1,2,4-triazol-3-yl]-2-methyl-2-butylamino}ethanol, 5-hydroxy-8-(1-hydroxy-2-isopropylaminobutyl)-2H-1,4-benzoxazin-3-(4H)-one, 1-(4-amino-3-chloro-5-trifluoromethylphenyl)-2-tert-

butylamino)ethanol and 1-(4-ethoxycarbonylamino-3-cyano-5-fluorophenyl)-2-(tert-butylamino)ethanol optionally in the form of their racemates, their enantiomers, their diastereomers, and mixtures thereof, and optionally their pharmacologically-compatible acid addition salts.

**[0031]** The preferred β2-agonists to be used in the combinations of the invention are: arformoterol, bambuterol, bitolterol, broxaterol, carbuterol, clenbuterol, dopexamine, fenoterol, formoterol, hexoprenaline, ibuterol, isoprenaline, levosalbutamol, mabuterol, meluadrine, nolomirole, orciprenaline, pirbuterol, procaterol, (R,R)-formoterol, reproterol, ritodrine, rimoterol, salbutamol, salmeterol, sibenadet, sulfonterol, terbutaline, tulobuterol, GSK-597901, milveterol, LAS100977 (5-(2-{[6-(2,2-difluoro-2-phenylethoxy)hexyl]amino}-1*(R)*-hydroxyethyl)-8-hydroxyquinolin-2(1*H*)-one), KUL-1248, carmoterol and indacaterol optionally in the form of their racemates, their enantiomers, their diastereomers, and mixtures thereof, and optionally their pharmacologically-compatible acid addition salts.

**[0032]** Since the M3 antagonists of the invention have a long duration of action, it is preferred that they are combined with long-acting β2-agonists (also known as LABAs). The combined drugs could thus be administered once or twice a day.

**[0033]** Particularly preferred LABAs are formoterol, salmeterol and GSK-597901, milveterol, LAS100977 (5-(2-{[6-(2,2-difluoro-2-phenylethoxy)hexyl]amino}-1*(R)*-hydroxyethyl)-8-hydroxyquinolin-2(1*H*)-one), KUL-1248, carmoterol and indacaterol optionally in the form of their racemates, their enantiomers, their diastereomers and mixtures thereof, and optionally their pharmacologically-compatible acid addition salts. More preferred are salmeterol, formoterol, LAS100977 (5-(2-{[6-(2,2-difluoro-2-phenylethoxy)hexyl]amino}-1*(R)*-hydroxyethyl)-8-hydroxyquinolin-2(1*H*)-one), and indacaterol. Still more preferred are salmeterol, formoterol and LAS100977 (5-(2-{[6-(2,2-difluoro-2-phenylethoxy)hexyl]amino}-1*(R)*-hydroxyethyl)-8-hydroxyquinolin-2(1*H*)-one), in particular salmeterol xinafoate,formoterol fumarate and LAS100977 (5-(2-{[6-(2,2-difluoro-2-phenylethoxy)hexyl]amino}-1*(R)*-hydroxyethyl)-8-hydroxyquinolin-2(1*H*)-one).

**[0034]** For example, the invention provides a pharmaceutical composition for inhalation comprising aclidinium in the form of a dry powder of a pharmaceutically acceptable salt, e.g., bromide, in admixture with a pharmaceutically acceptable carrier, e.g., lactose particles, together with formoterol fumarate, (i) comprising a single metered nominal dose of aclidinium equivalent

to about 400 μg aclidinium bromide together with a single metered nominal dose of about 5-25 μg (e.g. 6, 8.5, 12, 18 or 24 μg, for example 12 μg) formoterol fumarate or (ii) in a multidose dry powder inhaler device calibrated to provide a metered nominal dose of aclidinium equivalent to about 400 μg aclidinium bromide together with a meterd nominal dose of about 5-25 μg (e.g. 6, 8.5, 12, 18 or 24 μg, for example 12 μg) formotrol fumarate.

**[0035]** The pharmaceutical composition for inhalation comprising aclidinium and a β2-agonist, for example, formoterol or LAS100977 (5-(2-{[6-(2,2-difluoro-2-phenylethoxy)hexyl]amino}-1*(R)*-hydroxyethyl)-8-hydroxyquinolin-2(1*H*)-one), can be administered one or more times per day. Preferably once or twice a day.

**[0036]** Examples of suitable PDE4 inhibitors that can be combined with aclidinium in the present invention are benafentrine dimaleate, etazolate, denbufylline, rolipram, cipamfylline, zardaverine, arofylline, filaminast, tipelukast, tofimilast, piclamilast, tolafentrine, mesopram, drotaverine hydrochloride, lirimilast, roflumilast, cilomilast, oglemilast, apremilast, 6-[2-(3,4-Diethoxyphenyl)thiazol-4-yl]pyridine-2-carboxylic acid (tetomilast), (R)-(+)-4-[2-(3-Cyclopentyloxy-4-methoxyphenyl)-2-phenylethyl]pyridine (CDP-840), N-(3,5-Dichloro-4-pyridinyl)-2-[1-(4-fluorobenzyl)-5-hydroxy-1H-indol-3-yl]-2-oxoacetamide (GSK-842470), 9-(2-Fluorobenzyl)-N6-methyl-2-(trifluoromethyl)adenine (NCS-613), N-(3,5-Dichloro-4-pyridinyl)-8-methoxyquinoline-5-carboxamide (D-4418), N-[9-Methyl-4-oxo-1-phenyl-3,4,6,7-tetrahydropyrrolo[3,2,1-jk][1,4]benzodiazepin-3(R)-yl]pyridine-4-carboxamide, 3-[3-(Cyclopentyloxy)-4-methoxybenzyl]-6-(ethylamino)-8-isopropyl-3H-purine hydrochloride (V-11294A), 6-[3-(N,N-Dimethylcarbamoyl)phenylsulfonyl]-4-(3-methoxyphenylamino)-8-methylquinoline-3-carboxamide hydrochloride (GSK-256066), 4-[6,7-Diethoxy-2,3-bis(hydroxymethyl)naphthalen-1-yl]-1-(2-methoxyethyl)pyridin-2(1H)-one (T-440), (-)-trans-2-[3'-[3-(N-Cyclopropylcarbamoyl)-4-oxo-1,4-dihydro-1,8-naphthyridin-1-yl]-3-fluorobiphenyl-4-yl]cyclopropanecarboxylic acid (MK-0873), CDC-801, UK-500001, BLX-914, 2-carbomethoxy-4-cyano-4-(3-cyclopropylmethoxy-4-difluromethoxyphenyl)cyclohexan1-one, *cis* [4-cyano-4-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)cyclohexan-1-ol, 5(S)-[3-(Cyclopentyloxy)-4-methoxyphenyl]-3(S)-(3-methylbenzyl)piperidin-2-one (IPL-455903), ONO-6126 (Eur Respir J 2003, 22(Suppl. 45): Abst 2557) and the compounds claimed in the PCT patent applications number WO03/097613, WO2004/058729, WO 2005/049581, WO 2005/123693 and WO 2005/123692.

[0037] Examples of suitable corticosteroids and glucocorticoids that can be combined with aclidinium in the present invention are prednisolone, methylprednisolone, dexamethasone, dexamethasone cipecilate, naflocort, deflazacort, halopredone acetate, budesonide, beclomethasone dipropionate, hydrocortisone, triamcinolone acetonide, fluocinolone acetonide, fluocinonide, clocortolone pivalate, methylprednisolone aceponate, dexamethasone palmitoate, tipredane, hydrocortisone aceponate, prednicarbate, alclometasone dipropionate, Butixocort propionate, RPR-106541, halometasone, methylprednisolone suleptanate, mometasone furoate, rimexolone, prednisolone farnesylate, ciclesonide, deprodone propionate, fluticasone propionate, fluticasone furoate, halobetasol propionate, loteprednol etabonate, betamethasone butyrate propionate, flunisolide, prednisone, dexamethasone sodium phosphate, triamcinolone, betamethasone 17-valerate, betamethasone, betamethasone dipropionate, 21-Chloro-11beta-hydroxy-17alpha-[2-(methylsulfanyl)acetoxy]-4-pregnene-3,20-dione, Desisobutyrylciclesonide, hydrocortisone acetate, hydrocortisone sodium succinate, NS-126, prednisolone sodium phosphate, hydrocortisone probutate, prednisolone sodium metasulfobenzoate and clobetasol propionate, especially budesonide or mometasone.

[0038] For example, the invention provides a pharmaceutical composition for inhalation comprising aclidinium in the form of a dry powder of a pharmaceutically acceptable salt, e.g., bromide, in admixture with a pharmaceutically acceptable carrier, e.g., lactose particles, together with mometasone furoate, (i) comprising a single metered nominal dose of aclidinium equivalent to about 400 μg aclidinium bromide together with a single metered nominal dose of about 100-900 μg (e.g. , 100, 110, 200, 220, 300, 330, 400, 440, 800 or 880 μg, for example 200-450, e.g 220 or 440 μg) mometasone furoate, or (ii) in a multidose dry powder inhaler device calibrated to provide a metered nominal dose of aclidinium equivalent to about 400 μg aclidinium bromide together with a metered nominal dose of about 100-900 μg (e.g. 100, 110, 200, 220, 300, 330, 400, 440, 800 or 880 μg, for example 200-450, e.g 220 or 440 μg) mometasone furoate.

[0039] The pharmaceutical composition for inhalation comprising aclidinium and a corticosteroid, for example mometasone furoate, can be administered one or more times per a day. Preferably once or twice a day.

[0040] The invention also provides a pharmaceutical composition comprising aclidinium, a β2-agonist as defined above and a corticosteroid, as defined above. Most preferred β2-agonists are selected from LAS100977 ((5-(2-{[6-(2,2-difluoro-2-phenylethoxy)hexyl]amino}-1*(R)*-

hydroxyethyl)-8-hydroxyquinolin-2(1*H*)-one) and formoterol. Most preferred corticosteroid is a mometasone furoate. These triple combinations are suitable for administration once or twice a day.

EXAMPLE 1

**[0041]** Methods: Patients with moderate to severe stable COPD were randomized to receive double-blind, once-daily treatment with aclidinium (25, 50, 100, 200, or 400 μg), placebo, or open-label tiotropium 18 μg for 4 weeks. Spirometric measurements were performed at 22–24 h after the first dose and then at weekly intervals, and from 0.5–6 h post-administration on Day 1 and at Week 4 (Day 29).

**[0042]** Results: The ITT population included 460 patients. Aclidinium dose-dependently increased trough $FEV_1$ on Day 29 (table).

Mean change from baseline in trough $FEV_1$ on Day 29

| | Aclidinium (double-blind) | | | | | Tiotropium (open-label) |
|---|---|---|---|---|---|---|
| | 25 μg | 50 μg | 100 μg | 200 μg | 400 μg | 18 μg |
| n | 65 | 65 | 69 | 66 | 67 | 64 |
| Mean Δ, ml | 39 | 36 | 83 | 148* | 128* | 161* |

*p<0.05 vs placebo

**[0043]** Unlike tiotropium, the bronchodilatory effect of aclidinium during the first 6 h post-dose on Day 29 was comparable to that on Day 1 (all doses). Time to peak $FEV_1$ was achieved at 3 h post-dose for aclidinium 100–400 μg. Aclidinium was well tolerated, with no dose-dependent effect on ECG, laboratory parameters or adverse events.

**[0044]** Conclusion: Aclidinium produced sustained bronchodilation over 24 h and was well tolerated. Aclidinium 200 and 400 μg had comparable bronchodilatory effects to open-label tiotropium 18 μg. Based on the efficacy and tolerability data, aclidinium 400 μg is selected as the investigational dose for a future long-term clinical trial in COPD.

## CLAIMS

1. A pharmaceutical composition comprising aclidinium, or a pharmaceutically acceptable salt, in the form of a dry powder in admixture with a pharmaceutically acceptable dry powder carrier, the composition being adapted for use by inhalation in the treatment of asthma and/or chronic obstructive pulmonary disease, and wherein the composition is in a form for delivery at a metered nominal dose of aclidinium equivalent to about 400 µg aclidinium bromide.

2. The pharmaceutical composition according to claim 1, wherein the composition is in the form of a single-dose dry powder formulation comprising a single metered nominal dose of aclidinium equivalent to about 400 micrograms aclidinium bromide.

3. The pharmaceutical composition according to claim 1, wherein the composition is in the form of a multi-dose dry powder formulation for administration in a multi-dose dry powder inhaler device calibrated to provide metered nominal doses of aclidinium equivalent to about 400 micrograms aclidinium bromide.

4. The pharmaceutical composition according to any one of claims 1 to 3, wherein the pharmaceutically acceptable salt of aclidinium is aclidinium bromide.

5. The pharmaceutical composition according to any one of claims 1 to 4, wherein the pharmaceutically acceptable carrier is lactose particles.

6. The pharmaceutical composition according to any one of claims 1 to 5, wherein the ratio by weight of aclidinium to carrier is from 1:25 to 1:75.

7. The pharmaceutical composition according to claim 6 wherein the ratio by weight of aclidinium to carrier is from 1:50 to 1:75.

8. The pharmaceutical composition according to any one of claims 1 to 7, wherein the average particle diameter of the aclidinium is within 2-5 µm.

9. The pharmaceutical composition according to any one of claims 1 to 8, wherein the carrier particles have a d10 of 90 - 160 µm, a d50 of 170 – 270 µm, and d90 of 290 – 400 µm.

10. The pharmaceutical composition according to any one of claims 1 to 9, wherein the pharmaceutical composition further comprises one or more additional active agents, wherein said additional active agents are β2-agonists, PDE IV inhibitors, corticosteroids or a combination thereof.

11. The pharmaceutical composition according to claim 10, wherein the additional active agent is formoterol, salmeterol, budesonide, fluticasone propionate, or a combination thereof, in free or pharmaceutically acceptable salt form.

12. The pharmaceutical composition according to claim 11, wherein the additional active agent is formoterol fumarate in an amount of about 5-25 µg per dose.

13. The pharmaceutical composition according to claim 11, wherein the additional active agent is formoterol fumarate in an amount of about 6 µg per dose.

14. The pharmaceutical composition according to claim 11, wherein the additional active agent is formoterol fumarate in an amount of about 12 µg per dose.

15. Use of aclidinium in free or pharmaceutically acceptable salt form in the treatment of asthma and/or chronic obstructive pulmonary disease in a patient in need of such treatment, said aclidinium being in a form for administration by inhalation once or twice daily of a metered nominal dose of aclidinium equivalent to about 400 µg aclidinium bromide.

16. The use according to claim 15, wherein the aclidinium is in the form of a pharmaceutical composition according to any one of claims 1 to 14.

17. The use according to claim 15 or 16, further comprising the administration of one or more additional active agents, wherein said additional active agents are β2-agonists, PDE IV inhibitors, corticosteroids or a combination thereof.

18. The use according to claim 17, wherein the additional active agent is formoterol, salmeterol, budesonide, fluticasone propionate or a combination thereof, in free or pharmaceutically acceptable salt form.

19. The use according to claim 18, wherein the additional active agent is formoterol fumarate in an amount of about 5-25 µg per dose.

20. The use according to claim 18, wherein the additional active agent is formoterol fumarate in an amount of about 6 µg per dose.

21. The use according to claim 18, wherein the additional active agent is formoterol fumarate in an amount of about 12 µg per dose.

22. Use of aclidinium in free or pharmaceutically acceptable salt form in the manufacture of a medicament for treating asthma and/or chronic obstructive pulmonary disease in a patient in need of such treatment, said medicament being in a form for use by inhalation once or twice daily at a metered nominal dose of aclidinium equivalent to about 400 µg aclidinium bromide.

23. The use according to claim 22, wherein the medicament comprises the pharmaceutical composition according to any one of claims 1 to 14.

24. An inhalable dosage form comprising a dry powder pharmaceutical composition of aclidinium in the form of a dry powder of a pharmaceutically acceptable salt in admixture with a pharmaceutically acceptable dry powder carrier, wherein the dosage form is adapted to deliver a dose of aclidinium equivalent to about 400 µg aclidinium bromide.

25. The dosage form according to claim 24, wherein the pharmaceutical composition of aclidinium is in a form for administration by a powder inhaler device.

26. The dosage form according to claim 25, wherein the inhaler device is adapted to deliver a single-dose of the dry powder pharmaceutical composition in a single metered nominal dose of aclidinium equivalent to about 400 micrograms aclidinium bromide.

27. The dosage form according to claim 25, wherein the inhaler device is adapted to deliver multiple doses of the dry powder pharmaceutical composition, and wherein the inhaler device is calibrated to provide metered nominal doses of aclidinium equivalent to about 400 micrograms aclidinium bromide.

28. The dosage form according to any one of claims 24 to 27, wherein the pharmaceutically acceptable salt of aclidinium is aclidinium bromide.

29. The dosage form according to any one of claims 24 to 28, wherein the pharmaceutically acceptable carrier is lactose particles.

30. The dosage form according to any one of claims 24 to 29, wherein the ratio by weight of aclidinium to carrier is from 1:25 to 1:75.

31. The dosage form according to claim 30, wherein the ratio by weight of aclidinium to carrier is from 1:50 to 1:75.

32. The dosage form according to any one of claims 24 to 31, wherein the average particle diameter of the aclidinium is within 2-5 μm.

33. The dosage form according to any one of claims 24 to 32, wherein the carrier particles have a d10 of 90 - 160 μm, a d50 of 170 – 270 μm, and d90 of 290 – 400 μm.

34. The dosage form according to any one of claims 24 to 33, wherein the pharmaceutical composition further comprises one or more additional active agents, wherein said additional active agents are β2-agonists, PDE IV inhibitors, corticosteroids or a combination thereof.

35. The dosage form according to claim 34, wherein the additional active agent is formoterol, salmeterol, budesonide, fluticasone propionate, or a combination thereof, in free or pharmaceutically acceptable salt form.

36. The dosage form according to claim 35, wherein the additional active agent is formoterol fumarate in an amount of about 5-25 μg per dose.

37. The dosage form according to claim 35, wherein the additional active agent is formoterol fumarate in an amount of about 6 µg per dose.

38. The dosage form according to claim 35, wherein the additional active agent is formoterol fumarate in an amount of about 12 µg per dose.

39. The pharmaceutical composition according to any one of claims 1 to 14, wherein the metered nominal dose of aclidinium is equivalent to 400 µg +/-10% aclidinium bromide.

40. The use according to any one of claims 15 to 23, wherein the metered nominal dose of aclidinium is equivalent to 400 µg +/-10% aclidinium bromide.

41. The dosage form according to any one of claims 24 to 38, wherein the metered nominal dose of aclidinium is equivalent to 400 µg +/-10% aclidinium bromide.

42. A pharmaceutical composition comprising aclidinium, or a pharmaceutically acceptable salt thereof, in the form of a dry powder in admixture with a pharmaceutically acceptable dry powder carrier, the composition being adapted for use by inhalation in the treatment of asthma and/or chronic obstructive pulmonary disease, and wherein the composition is in a form for delivery at an emitted dose of aclidinium equivalent to 360 µg +/- 35% aclidinium bromide.

43. The pharmaceutical composition according to claim 42, wherein the composition is in the form of a single-dose dry powder formulation comprising a single emitted dose of aclidinium equivalent to 360 µg +/- 35% aclidinium bromide.

44. The pharmaceutical composition according to claim 42, wherein the composition is in the form of a multi-dose dry powder formulation for administration in a multidose dry powder inhaler device calibrated to provide emitted doses of aclidinium equivalent to 360 µg +/- 35% aclidinium bromide.

45. The pharmaceutical composition according to any of claims 42 to 44, wherein the pharmaceutically acceptable salt of aclidinium is aclidinium bromide.

46. The pharmaceutical composition according to any of claims 42 to 45, wherein the pharmaceutically acceptable carrier is lactose particles.

47. The pharmaceutical composition according to any one claims 42 to 46, wherein the ratio by weight of aclidinium to carrier is from 1:25 to 1:75.

48. The pharmaceutical composition according to claim 47, wherein the ratio by weight of aclidinium to carrier is from 1:50 to 1:75.

49. The pharmaceutical composition according to any of claims 42 to 48, wherein the average particle diameter of the aclidinium is within 2-5μm.

50. The pharmaceutical composition according to any of claims 42 to 49, wherein the carrier particles have a d10 of 90 - 160 μm, a d50 of 170 – 270 μm, and d90 of 290 – 400 μm.

51. The pharmaceutical composition according to any one of claims 42 to 50, wherein the pharmaceutical composition further comprises an effective amount of one or more additional active agents selected from β2-agonists, PDE IV inhibitors, and corticosteroids.

52. The pharmaceutical composition according to claim 51, wherein the additional active agent is selected from formoterol, salmeterol, budesonide, and fluticasone propionate, in free or pharmaceutically acceptable salt form.

53. The pharmaceutical composition according to claim 52, wherein the additional active agent is formoterol fumarate in an amount of 5-25 μg per nominal dose.

54. The pharmaceutical composition according to claim 52, wherein the additional active agent is formoterol fumarate in an amount of 6 μg per nominal dose.

55. The pharmaceutical composition according to claim 52, wherein (c) the additional active agent is formoterol fumarate in an amount of 12 μg per nominal dose.

56. Use of aclidinium in free or pharmaceutically acceptable salt form in the treatment of asthma and/or chronic obstructive pulmonary disease in a patient in need of such treatment, said aclidinium being in a form for administration by inhalation once or twice daily of an emitted dose of aclidinium equivalent to about 360 µg +/- 35% aclidinium bromide.

57. The use according to claim 56, wherein the aclidinium is in the form of a pharmaceutical composition according to any one of claims 42 to 55.

58. The use according to claim 56 or 57 further comprising the use of one or more additional active agents, wherein the additional active agents are β2-agonists, PDE IV inhibitors, corticosteroids or a combination thereof.

59. The use according to claim 58, wherein the additional active agent is formoterol, salmeterol, budesonide, fluticasone propionate or a combination thereof in free or pharmaceutically acceptable salt form.

60. The use according to claim 59, wherein the additional active agent is formoterol fumarate in an amount of 5-25 µg per nominal dose.

61. The use according to claim 59, wherein the additional active agent is formoterol fumarate in an amount of 6 µg per nominal dose.

62. The use according to claim 59, wherein the additional active agent is formoterol fumarate in an amount of 12 µg per nominal dose.

63. Use of aclidinium in free or pharmaceutically acceptable salt form in the manufacture of a medicament for treating asthma and/or chronic obstructive pulmonary disease in a patient in need of such treatment, said use medicament being in a form for use by inhalation once or twice daily at an emitted dose of aclidinium equivalent to 360 µg +/- 35% aclidinium bromide.

64. The use according to claim 63, wherein the aclidinium is in the form of a pharmaceutical composition according to any one of claims 42 to 55.

65. An inhalable dosage form comprising a dry powder pharmaceutical composition of aclidinium, or a pharmaceutically acceptable salt thereof, in the form of a dry powder of a pharmaceutically acceptable salt in admixture with a pharmaceutically acceptable dry powder carrier, wherein the dosage form is adapted to deliver an emitted dose of aclidinium equivalent to about 360 µg +/- 35% aclidinium bromide.

66. A pharmaceutical composition comprising aclidinium, or a pharmaceutically acceptable salt thereof, in the form of a dry powder in admixture with a pharmaceutically acceptable dry powder carrier, the composition being adapted for use by inhalation in the treatment of asthma and/or chronic obstructive pulmonary disease, and wherein the composition is in a form for delivery at a fine particle dose of aclidinium equivalent to 120 µg +/- 35% aclidinium bromide.

67. The pharmaceutical composition according to claim 66, wherein the composition is in the form of a single-dose dry powder formulation comprising a fine particle dose of aclidinium equivalent to 120 µg +/- 35% aclidinium bromide.

68. The pharmaceutical composition according to claim 66, wherein the composition is in the form of a multi-dose dry powder formulation for administration in a multidose dry powder inhaler device calibrated to provide fine particle doses of aclidinium equivalent to 120 µg +/- 35% aclidinium bromide.

69. The pharmaceutical composition according to any of claims 66 to 68, wherein the pharmaceutically acceptable salt of aclidinium is aclidinium bromide.

70. The pharmaceutical composition according to any of claims 66 to 69, wherein the pharmaceutically acceptable carrier is lactose particles.

71. The pharmaceutical composition according to any one claims 66 to 70, wherein the ratio by weight of aclidinium to carrier is from 1:25 to 1:75.

72. The pharmaceutical composition according to claim 71, wherein the ratio by weight of aclidinium to carrier is from 1:50 to 1:75.

73. The pharmaceutical composition according to any of claims 66 to 71, wherein the average particle diameter of the aclidinium is within 2-5μm.

74. The pharmaceutical composition according to any of claims 66 to 71, wherein the carrier particles have a d10 of 90 - 160 μm, a d50 of 170 – 270 μm, and d90 of 290 – 400 μm.

75. The pharmaceutical composition according to any one of claims 66 to 74, wherein the pharmaceutical composition further comprises an effective amount of one or more additional active agents selected from β2-agonists, PDE IV inhibitors, and corticosteroids.

76. The pharmaceutical composition according to claim 75, wherein the additional active agent is selected from formoterol, salmeterol, budesonide, and fluticasone propionate, in free or pharmaceutically acceptable salt form.

77. The pharmaceutical composition according to claim 76, wherein the additional active agent is formoterol fumarate in an amount of 5-25 μg per nominal dose.

78. The pharmaceutical composition according to claim 76, wherein the additional active agent is formoterol fumarate in an amount of 6 μg per nominal dose.

79. The pharmaceutical composition according to claim 76, wherein (c) the additional active agent is formoterol fumarate in an amount of 12 μg per nominal dose.

80. Use of aclidinium in free or pharmaceutically acceptable salt form in the treatment of asthma and/or chronic obstructive pulmonary disease in a patient in need of such treatment, said aclidinium being in a form for administration by inhalation once or twice daily of a fine particle dose of aclidinium equivalent to 120 μg +/- 35% aclidinium bromide.

81. The use according to claim 80, wherein the aclidinium is in the form of a pharmaceutical composition according to any one of claims 66 to 79.

82. The use according to claim 80 or 81 further comprising the use of one or more additional active agents, wherein the additional active agents are β2-agonists, PDE IV inhibitors, corticosteroids or a combination thereof.

83. The use according to claim 82, wherein the additional active agent is formoterol, salmeterol, budesonide, fluticasone propionate or a combination thereof in free or pharmaceutically acceptable salt form.

84. The use according to claim 83, wherein the additional active agent is formoterol fumarate in an amount of 5-25 µg per nominal dose.

85. The use according to claim 83, wherein the additional active agent is formoterol fumarate in an amount of 6 µg per nominal dose.

86. The use according to claim 83, wherein the additional active agent is formoterol fumarate in an amount of 12 µg per nominal dose.

87. Use of aclidinium in free or pharmaceutically acceptable salt form in the manufacture of a medicament for treating asthma and/or chronic obstructive pulmonary disease in a patient in need of such treatment, said use medicament being in a form for use by inhalation once or twice daily at a fine particle dose of aclidinium equivalent to 120 µg +/- 35% aclidinium bromide.

88. The use according to claim 87, wherein the aclidinium is in the form of a pharmaceutical composition according to any one of claims 66 to 79.

89. An inhalable dosage form comprising a dry powder pharmaceutical composition of aclidinium or a pharmaceutically acceptable salt thereof, in the form of a dry powder in admixture with a pharmaceutically acceptable dry powder carrier, wherein the dosage form is adapted to deliver a fine particle dose of aclidinium equivalent to 120 µg +/- 35% aclidinium bromide.