Therapeutic agents useful for treating pulmonary disorders are advantageously administered directly into the respiratory tract by inhalation. In this regard, several types of pharmaceutical inhalation devices have been developed for administering therapeutic agents by inhalation, including dry powder inhalers (DPI), metered-dose inhalers (MDI) and nebulizer inhalers. When preparing pharmaceutical compositions and formulations for use in such devices, it is highly desirable to have a crystalline form of the therapeutic agent that is neither hygroscopic nor deliquescent and which has a relatively high melting point (i.e. greater than about 150°C), thereby allowing the material to be micronized without significant decomposition or loss of crystallinity . International Patent application no PCT/US2004/004449, publication no. WO2004/074246 A2 (Theravance Inc, South San Francisco, California, US), at page 135, as Example 35, describes the preparation of the compound of formula I, as the di- trifiuoroacetate salt, in a lyophilised form.

International Patent application no PCT/US2005/029013, publication no. WO 2006/023454 , filed 15 Aug 2005, (Theravance Inc, South San Francisco, California, US) describes crystalline 1 ,2-ethanedisulfonic acid salts of the compound of formula I.

There remains the need to identify further stable, non-deliquescent, crystalline salt forms of the compound of formula I which have an acceptable level of hygroscopicity and a relatively high melting point.

SUMMARY ~~OF THE INVENTION~~

The present ~~invention~~ disclosure provides a succinic acid salt of biphenyl-2-ylcarbamic acid l-[2-(2-chloro-4-{[(R)-2-hydroxy-2-(8-hydroxy-2-oxo-l,2-dihydroquinolin-5-yl)ethylamino]methyl} -5-methoxyphenylcarbamoyl)ethyl]piperidin-4-yl ester, in particular a crystalline solid state form thereof, or a solvate thereof.

In one embodiment, a crystalline form of the salt of the present ~~invention~~disclosure, hereinafter referred to as Form 1, has a melting point greater than about 170 <0>C and has been found not to be deliquescent, even when exposed to atmospheric moisture. Further crystalline salt forms, hereinafter referred to as Form 2 and 3, have also been identified.

Among other uses, a succinic acid salt of the compound of formula I is useful for preparing pharmaceutical compositions which are expected to be useful for treating pulmonary disorders. Accordingly, in a further embodiment, ~~the present invention provides~~there is provided a pharmaceutical composition comprising a pharmaceutically acceptable carrier

and a succinic acid salt of biphenyl-2-ylcarbamic acid l-[2-(2-chloro-4-{[(*R*)-2-hydroxy- 2-(8-hydroxy-2-oxo-l,2-dihydroquinolin-5-yl)ethylamino]methyl}-5-methoxyphenylcarbamoyl)ethyl]piperidin-4-yl ester, in particular a crystalline solid state form thereof, or a solvate thereof.

In a particular embodiment, the pharmaceutical composition of this ~~invention~~ disclosure further comprises a steroidal anti-inflammatory agent, such as a cortecosteroid; a muscarinic antagonist or a phosphodiesterase-4 inhibitor; or a combination thereof.

In another embodiment, this ~~invention~~ disclosure provides a pharmaceutical composition comprising an aqueous isotonic saline solution comprising a succinic acid salt of biphenyl-2-ylcarbamic acid l-[2-(2-chloro-4-{[(R)-2-hydroxy-2-(8-hydroxy-2-oxo-l,2-dihydroquinolin-5-yl)ethylamino]methyl}-5-methoxyphenylcarbamoyl)ethyl]piperidin-4- yl ester, wherein the solution has a pH in the range of from about 4 to about 6.

In yet another embodiment, this ~~invention~~ disclosure provides a combination comprising:

(a) a succinic acid salt of biphenyl-2-ylcarbamic acid l-[2-(2-chloro-4- {[(*R*)- 2-hydroxy-2-(8-hydroxy-2-oxo-l,2-dihydroquinolin-5-yl)ethylamino]methyl}-5-methoxyphenylcarbamoyl)ethyl]piperidin-4-yl ester, in particular a crystalline solid state form thereof, or a solvate thereof; and

(b) a steroidal anti-inflammatory agent.

The compound of formula I has both muscarinic antagonist and β_2 adrenergic receptor agonist activity. Accordingly, a succinic acid salt of this ~~invention~~ disclosure is expected to be useful as a therapeutic agent for treating pulmonary disorders, such as asthma and chronic obstructive pulmonary disease.

Accordingly, ~~in one of its method aspects,~~ this ~~invention~~ disclosure provides a method for treating a pulmonary disorder, the method comprising administering to a patient in need of treatment a therapeutically effective amount of a succinic acid salt of biphenyl-2-ylcarbamic acid l-[2-(2-chloro-4-{[(R)-2-hydroxy-2-(8-hydroxy-2-oxo-l,2- dihydroquinolin-5-yl)ethylamino]methyl}-5-methoxyphenylcarbamoyl)ethyl]piperidin-4- yl ester or a solvate thereof.

Additionally, ~~in another of its method aspects,~~ this ~~invention~~ disclosure provides a method of producing bronchodilation in a patient, the method comprising administering by inhalation to the patient a bronchodilation-producing amount of a succinic acid salt of biphenyl-2-ylcarbamic acid l-[2-(2-chloro-4-{[(R)-2-hydroxy-2-(8-hydroxy-2-oxo-l,2-

dihydroquinolin-5-yl)ethylamino]methyl}-5-methoxyphenylcarbamoyl)ethyl]-piperidin- 4-yl ester or a solvate thereof.

This ~~invention~~ disclosure also provides a method of treating chronic obstructive pulmonary disease or asthma, the method comprising administering to a patient in need of treatment a therapeutically effective amount of a succinic acid salt of biphenyl-2-ylcarbamic acid 1- [2-(2-chloro-4-{[(R)-2-hydroxy-2-(8-hydroxy-2-oxo-l,2-dihydroquinolin-5-yl)ethylamino]methyl}-5-methoxyphenylcarbamoyl)ethyl]piperidin-4-yl ester or a solvate thereof.

This ~~invention~~ disclosure is also directed to processes for preparing a succinic acid salt of the compound of formula I, in particular a crystalline form thereof.

Accordingly, this ~~invention~~ disclosure provides a process for preparing a succinic acid salt of biphenyl-2-ylcarbamic acid l-[2-(2-chloro-4-{[(R)-2-hydroxy-2-(8-hydroxy-2-oxo-l,2-dihydroquinolin-5-yl)ethylamino]methyl}-5-methoxyphenylcarbamoyl)ethyl]piperidin-4- yl ester or a solvate thereof; the process comprising contacting biphenyl-2-ylcarbamic acid l-[2-(2-chloro-4-{[(R)-2-hydroxy-2-(8-hydroxy-2-oxo-l,2-dihydroquinolin-5-yl)ethylamino]methyl} -5-methoxyphenylcarbamoyl)ethyl]piperidin-4-yl ester with succinic acid.

This salt formation step may be conveniently carried out using the corresponding free base prepared from the corresponding tri-alkyl silyloxy-protected precursor, without the need for full isolation of the free base intermediate.

This ~~invention~~ disclosure is also directed to a succinic acid salt of biphenyl-2-ylcarbamic acid l-[2-(2-chloro-4-{[(R)-2-hydroxy-2-(8-hydroxy-2-oxo-l,2-dihydroquinolin-5-yl)ethylamino]methyl}-5-methoxyphenylcarbamoyl)ethyl]piperidin-4-yl ester, or a crystalline solid state form thereof, or a solvate thereof, for use in therapy or as a medicament.

Additionally, this ~~invention~~ disclosure is directed to the use of a succinic acid salt of biphenyl-2-ylcarbamic acid l-[2-(2-chloro-4-{[(R)-2-hydroxy-2-(8-hydroxy-2-oxo-l,2-dihydroquinolin-5-yl)ethylamino]methyl}-5-methoxyphenylcarbamoyl)ethyl]piperidin-4- yl ester, or a crystalline solid state form thereof, or a solvate thereof for the manufacture of a medicament; especially for the manufacture of a medicament for the treatment of a pulmonary disorder.

This ~~invention~~ disclosure is also directed to the use of:

(a) a succinic acid salt of biphenyl-2-ylcarbamic acid l-[2-(2-chloro-4-{[(R)- 2-hydroxy-2-(8-hydroxy-2-oxo-l,2-dihydroquinolin-5-yl)ethylamino]methyl}-5-methoxyphenylcarbamoyl)ethyl]piperidin-4-yl ester, or a crystalline solid state form thereof, or a solvate thereof; and

(b) a steroidal anti-inflammatory agent; in the manufacture of a medicament for the treatment of a pulmonary disorder.

This ~~invention~~ disclosure is also directed to a succinic acid salt of biphenyl-2-ylcarbamic acid l-[2-(2-chloro-4-{[(R)-2-hydroxy-2-(8-hydroxy-2-oxo-l,2-dihydroquinolin-5-yl)ethylamino]methyl}-5-methoxyphenylcarbamoyl)ethyl]piperidin-4-yl ester, or a crystalline solid state form thereof, or a solvate thereof, in micronized form; and to pharmaceutical compositions comprising a pharmaceutically acceptable carrier and a succinic acid salt of biphenyl-2-ylcarbamic acid l-[2-(2-chloro-4-{[(R)-2-hydroxy-2-(8- hydroxy-2-oxo- 1 ,2-dihydroquinolin-5-yl)ethylamino]methyl} -5- methoxyphenylcarbamoyl)ethyl]-piperidin-4-yl ester, or a crystalline solid state form thereof, or a solvate thereof, in micronized form.

In accordance with a first aspect of the present disclosure, there is provided a succinic acid salt of biphenyl-2-ylcarbamic acid 1-[2-(2-chloro-4-{[(*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]methyl}-5-methoxyphenylcarbamoyl)ethyl]piperidin-4-yl ester or a solvate thereof, which is the Form 1 crystalline solid state form characterized by an x-ray powder diffraction pattern having diffraction peaks at 2θ values of:

2θ
5.0
5.7
7.1
10.0
12.6
13.8
14.4
15.5
16.1
16.4
16.9
17.8
18.5
20.2
20.5
21.4
25.3
25.8
26.3

In accordance with a second aspect of the present disclosure, there is provided a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a salt as disclosed herein.

In accordance with a third aspect of the present disclosure, there is provided a combination comprising: (a) a salt as disclosed herein; and (b) a steroidal anti-inflammatory agent.

In accordance with a fourth aspect of the present disclosure, there is provided a succinic acid salt of biphenyl-2-ylcarbamic acid 1-[2-(2-chloro-4-{[(*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]methyl}-5-methoxyphenylcarbamoyl)ethyl]piperidin-4-yl ester or a solvate thereof, as disclosed herein, for use in therapy or as a medicament.

In accordance with a fifth aspect of the present disclosure, there is provided use of a succinic acid salt of biphenyl-2-ylcarbamic acid 1-[2-(2-chloro-4-{[(*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]methyl}-5-methoxyphenylcarbamoyl)ethyl]piperidin-4-yl ester or a solvate thereof, as disclosed herein, in the manufacture of a medicament for the treatment of a pulmonary disorder selected from: chronic obstructive pulmonary disease, asthma, pulmonary fibrosis, allergic rhinitis and rhinorrhea.

In accordance with a sixth aspect of the present disclosure, there is provided use of: (a) a succinic acid salt of biphenyl-2-ylcarbamic acid 1-[2-(2-chloro-4-{[(*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]methyl}-5-methoxyphenylcarbamoyl)ethyl]piperidin-4-yl ester or a solvate thereof, as disclosed herein; and (b) a steroidal anti-inflammatory agent; in the manufacture of a medicament for the treatment of a pulmonary disorder selected from: chronic obstructive pulmonary disease, asthma, pulmonary fibrosis, allergic rhinitis and rhinorrhea.

In accordance with a seventh aspect of the present disclosure, there is provided a process for preparing the Form 1 succinate salt, as disclosed herein, which process comprises the steps: dissolving the succinate salt in aqueous THF (10-18%, for example 10-16%), at a temperature in the range 18 to 23°C, for example about 20°C; adding a first volume of a lower alcohol which is either ethanol or isopropanol, in particular isopropanol, and warming to 32-40°C; optionally seeding with Form 1; adding a second volume of the lower alcohol, for

example over several hours, preferably about 12 h; cooling to temperature in the range 18 to 23°C, for example about 20 °C; and collecting the crystalline product.

BRIEF DESCRIPTION OF THE DRAWINGS

Various aspects of the present invention are illustrated by reference to the accompanying drawings.

Figure 1 shows a differential scanning calorimetry (DSC) trace for a sample of a first crystalline solid state form of a succinic acid salt of biphenyl-2-ylcarbamic acid l-[2- (2-chloro-4-{[(R)-2-hydroxy-2-(8-hydroxy-2-oxo-l,2-dihydroquinolin-5- yl)ethylamino]methyl} -5-methoxyphenylcarbamoyl)ethyl]piperidin-4-yl ester of this invention, hereinafter referred to as Form 1.

Figure 2 shows a differential scanning calorimetry (DSC) trace for a sample of a second crystalline solid state form of a succinic acid salt of biphenyl-2-ylcarbamic acid 1- [2-(2-chloro-4-{[(R)-2-hydroxy-2-(8-hydroxy-2-oxo-l,2-dihydroquinolin-5-yl)ethylamino]methyl} -5-methoxyphenylcarbamoyl)ethyl]piperidin-4-yl ester of this invention, hereinafter referred to as Form 2.

Figure 3 shows a differential scanning calorimetry (DSC) trace for a sample of a third crystalline solid state form of a succinic acid salt of biphenyl-2-ylcarbamic acid 1- [2-(2-chloro-4-{[(R)-2-hydroxy-2-(8-hydroxy-2-oxo-l,2-dihydroquinolin-5-