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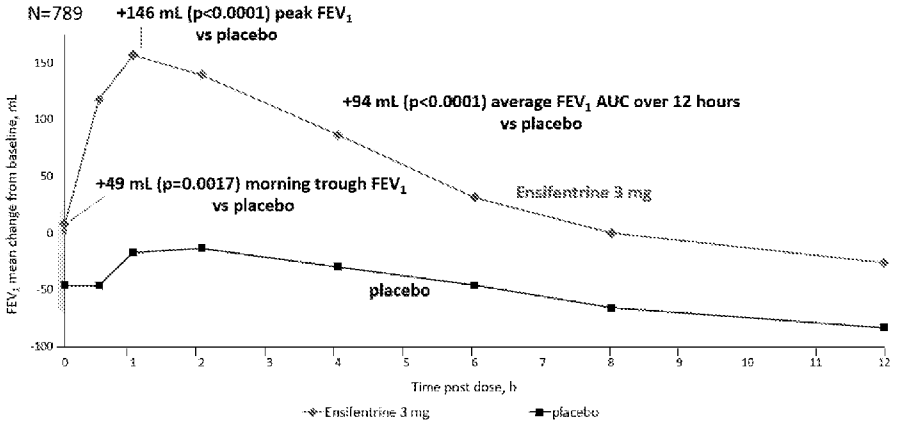


FIGURE 1

(57) Abstract: The present invention relates to a compound for use in treating moderate COPD in a patient, which compound is ensifentrine or a pharmaceutically acceptable salt thereof.

WO 2024/033624 A1

ENSIFENTRINE (RPL-554) FOR THE TREATMENT OF MODERATE CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)

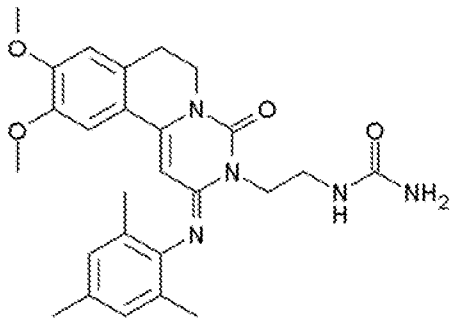
FIELD OF THE INVENTION

The present invention relates to the treatment of moderate chronic obstructive pulmonary disease (COPD).

BACKGROUND OF THE INVENTION

Ensifentrine (*N*-(2-{(2*E*)-9,10-dimethoxy-4-oxo-2-[(2,4,6-trimethylphenyl)imino]-6,7-dihydro-2*H*-pyrimido[6,1-*a*]isoquinolin-3(4*H*)-yl}ethyl)urea; also known as RPL554) is a dual PDE3/PDE4 inhibitor and is described in WO 00/58308 A1.

As a combined PDE3/PDE4 inhibitor, ensifentrine has both bronchodilatory and anti-inflammatory activity and is useful in the treatment of respiratory disorders including chronic obstructive pulmonary disease (COPD). The chemical structure of ensifentrine is shown below.



COPD is a progressive, long-term condition and can be experienced by patients at different levels of severity. The symptoms of COPD can range from mild to severe, and different treatment options can be preferred for different severities of COPD.

It would be beneficial to develop a treatment which is particularly effective for moderate COPD.

SUMMARY OF THE INVENTION

It is a surprising finding of the present invention that, while ensifentrine is effective in treating all forms of COPD, it has been found to be particularly effective in treating moderate COPD. Inhaled administration of ensifentrine has been found to cause a

particularly significant increase in FEV_1 (forced expiratory volume in 1 second) in patients with moderate COPD.

There are a number of drugs which are disclosed for use in treating COPD. These drugs have different efficacy profiles against different grades and subtypes of COPD.

The invention accordingly provides a compound for use in treating moderate COPD in a patient, which compound is ensifentrine or a pharmaceutically acceptable salt thereof.

The invention also provides a method of treating moderate COPD in a patient, which method comprises administering a therapeutically effective amount of a compound which is ensifentrine or a pharmaceutically acceptable salt thereof to the patient.

Further provided by the invention is use of a compound which is ensifentrine or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating moderate COPD.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1 shows the FEV_1 profile over 12 hours at Week 12.

DETAILED DESCRIPTION OF THE INVENTION

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) classifies COPD into four distinct stages. These are mild COPD, moderate COPD, severe COPD or very severe COPD. The 2022 COPD report is published by the Global Initiative for Chronic Obstructive Disease, Inc, and that document is incorporated by reference in its entirety.

The above stages of COPD can be classified as set out below, where FEV_1 is forced expiratory volume in 1 second and FVC is forced vital capacity.

- Mild COPD: $FEV_1/FVC < 0.7$ and $FEV_1 \geq 80$ % predicted
- Moderate COPD: $FEV_1/FVC < 0.7$ and $50\ \% \leq FEV_1 < 80$ % predicted
- Severe COPD: $FEV_1/FVC < 0.7$ and $30\ \% \leq FEV_1 < 50$ % predicted
- Very Severe COPD: $FEV_1/FVC < 0.7$ and $FEV_1 < 30$ % predicted

In each case the actual FEV_1 for the patient is compared with a predicted FEV_1 value based on factors such as age and height of the patient. These predicted values are readily available to the skilled person, for instance from the National Health and Nutrition Examination Survey III (Hankinson JL, Odencrantz JR, Fedan KB. Spirometry reference values from a sample of the general U.S. Population. Am J Respir Crit Care. 1999;159:179-187). Examples of equations for calculating the predicted FEV_1 (in L) for a patient are as follows, where H is height (cm) and A is age (yrs):

- Males: 0.0430H - 0.0290A - 2.490
- Females: 0.0395H - 0.025A - 2.600

The FEV_1 and FVC used to determine the severity of COPD in a patient are measured by carrying out spirometry shortly after the administration of an adequate dose of at least one short-acting inhaled bronchodilator. Typically, measurement of FEV_1 and FVC for determining COPD disease severity is done between 15 and 30 minutes following administration of salbutamol (albuterol).

Typically, as used herein, FEV_1 and FVC are determined as set out in the article Standardisation of spirometry, Eur J 2005; 26; 319-338.

The patient may accordingly have been determined to have moderate COPD by measuring $FEV_1/FVC < 0.7$ and $50\ \% \leq FEV1 < 80\ \%$ predicted FEV_1 value, where FEV_1 is forced expiratory volume in 1 second and FVC is forced vital capacity as measured between 15 and 30 minutes after a dose of a bronchodilator, optionally wherein the bronchodilator is salbutamol. The determination of the patient's COPD severity may take place at least 1 day prior to the first administration of the compound.

The patient may be male. The patient may be female. The patient may have an age of greater than or equal to 65 years. The patient may have an age of less than 65 years. The patient may be taking a background medication selected from one or more of a long-acting muscarinic antagonist (LAMA), a long-acting beta-agonist (LABA) and an inhaled corticosteroid (ICS). In some cases, the patient is not receiving a background medication. For instance, the patient may not be taking a

background medication, which background medication is a long-acting muscarinic antagonist (LAMA), a long-acting beta-agonist (LABA) or an inhaled corticosteroid (ICS).

The compound is ensifentrine or a pharmaceutically acceptable salt thereof. Pharmaceutically acceptable salts are well known to the skilled person. Typically, the compound is ensifentrine (i.e. ensifentrine free base).

The method typically comprises administering the compound to the patient by inhalation. A pharmaceutical composition comprising the compound and one or more pharmaceutically acceptable excipients or diluents is typically administered to the patient by inhalation, for instance by nebuliser, pressurised metered dose inhaler (pMDI) or dry powder inhaler (DPI).

Preferably, the method comprises administering the compound to the patient by inhalation from a nebuliser. Nebulisers aerosolise a liquid pharmaceutical composition into an aerosol that is inhaled into a patient's respiratory tract. Examples of nebulisers include a soft mist nebuliser, a vibrating mesh nebuliser, a jet nebuliser and an ultrasonic wave nebuliser. Suitable nebuliser devices include the Philips I-neb™ (Philips), the Philips SideStream (Philips), the AeroNeb® (Philips), the Philips InnoSpire Go (Philips), the Pari LC Sprint (Pari GmbH), the AERxR™ Pulmonary Delivery System (Aradigm Corp) and the Pari LC Plus Reusable Nebuliser (Pari GmbH). The nebulizer may for instance be a PARI LC Sprint jet nebulizer with a PARI Vios® PRO Aerosol Delivery System PARI BOY® compressor. The compound may be inhaled via the nebuliser for from 1 to 15 minutes.

Typically, the method comprises administering the compound to the patient once, twice or three times per day, for instance twice or three times per day. The compound may be administered to the patient by inhalation once, twice or three times a day. Preferably the method comprises administering the compound to the patient by inhalation twice a day. The method may comprise administering a first dose of the compound in the morning (for instance within 3 hours following waking) and a second dose of the compound in the evening (for instance within 3 hours before bed). Typically, the morning and evening doses are administered from 10 to 14 hours apart, for instance about 12 hours apart.

The compound may be used in any suitable therapeutically effective amount. Typically, the daily dose of the compound is from 0.1 to 20 mg. Typically, the method comprises administering a total daily dose of the compound of from 0.5 to 10 mg. Preferably, the total daily dose of the compound (e.g. ensifentrine free base) is from 5 to 7 mg, for instance about 6 mg per day. As used herein, the term "about" may represent a variation of ± 10% of the stated value. The total daily dose of the compound may be 6.0 mg.

Typically, the compound is administered twice a day in two separate doses which are the same or similar. For instance, the method may comprise administering the compound to the patient twice a day in a first dose of from 1 to 5 mg and a second dose of from 1 to 5 mg. Typically, the method may comprise administering the compound to the patient twice a day in a first dose of from 2 to 4 mg and a second dose of from 2 to 4 mg.

Preferably, the method comprises administering two doses of about 3 mg ensifentrine free base to the patient per day by inhalation. The method preferably comprises administering a dose of about 3 mg of the compound to the patient twice a day (3 mg BID) by inhalation. More preferably, the method comprises administering by nebuliser a dose of about 3 mg the compound to the patient twice a day. Each dose may be 3.0 mg free base ensifentrine administered by nebulizer.

The compound is typically used as a maintenance therapy. Typically, the method comprises administering the compound to the patient at least once per day for at least 8 weeks. The compound may be administered to the patient at least once per day for at least 16 weeks, preferably for at least 24 weeks. The compound may be administered daily to the patient for at least 1 year. The method may comprise administering the compound to the patient at least once every 24 hours, preferably at least twice every 24 hours, for at least 8 weeks, preferably for at least 16 weeks, more preferably for at least 24 weeks.

The compound is preferably administered as a suspension formulation, i.e. a suspension of particles comprising the compound in a diluent. The compound may alternatively be delivered as a dry powder, for instance a dry powder comprising particles comprising the compound and particles of a carrier such as lactose.

The method typically comprises administering an inhalable pharmaceutical composition comprising a suspension of particles of the compound in a diluent. The particles comprising the compound typically have a particle size distribution with a Dv50 of from 0.5 μm to 5.0 μm. The particles preferably have a Dv50 of from 1.0 μm to 2.0 μm.

Particle sizes are described herein by reference to the Dv50 value, which is the median particle size for a volume distribution. Thus, half the volume of the particles have diameters of less than the Dv50 value and half the volume of the particles have diameters of greater than the Dv50 value. This is a well-known manner in which to describe particle size distributions.

The technique used to measure the Dv50 values as stated herein is typically laser diffraction. The particle size distribution of the particles comprising the compound may be as measured by laser diffraction using a wet powder dispersion system. For instance, the particle size distribution can be measured by laser diffraction using a Malvern Spraytec in conjunction with a wet dispersion cell. Typically, the instrument parameters for the Malvern Spraytec are as follows:

- particle – standard opaque particle;
- refractive index Particle – 1.50;
- refractive index (imaginary) – 0.50;
- density of particle – 1.00;
- refractive index of dispersant – 1.33;
- controller unit – 1000RPM;
- measurement type – timed;
- initial sampling time – 30s;
- obscuration – 20% - 30%;
- dispersant – 1% Polysorbate 20 in deionised water.

The particles comprising the compound typically comprise ensifentrine (i.e. ensifentrine free base). The particles may comprise at least 90 wt% ensifentrine free base relative to the total weight of the particles. The particles may comprise at least 99 wt% ensifentrine. The particles may consist of ensifentrine.

The concentration of particles comprising the compound in the inhalable pharmaceutical composition is typically from 0.1 to 5.0 mg/mL, preferably from 0.1 to 2.5 mg/mL, more preferably from 1.0 to 2.0 mg/mL.

The inhalable pharmaceutical composition typically further comprises one or more tonicity adjusters, one or more buffers and one or more surfactants. The tonicity adjuster is typically sodium chloride.

Examples of buffers include a citrate buffer, a phosphate buffer, an acetate buffer, and a bicarbonate buffer. Preferably, the buffer is a phosphate buffer, for instance sodium dihydrogen phosphate dihydrate and/or disodium phosphate dihydrate.

Examples of surfactants include lecithin, oleic acid, polyoxyethylene glycol alkyl ethers (for instance PEG 300, PEG 600, PEG 1000, Brij 30, Brij 35, Brij 56, Brij 76 and Brij 97), polypropylene glycol (for instance PPG 2000), glucoside alkyl ethers, polyoxyethylene glycol octylphenol ethers, polyoxyethylene glycol alkylphenol ethers, glycerol alkyl esters, polyoxyethylene glycol sorbitan alkyl esters (polysorbates, for instance polysorbate 20, polysorbate 40, polysorbate 60 and polysorbate 80), sorbitan alkyl esters (for instance sorbitan monolaurate (Span 20), sorbitan monooleate (Span 80) and sorbitan trioleate (Span 85)), cocamide MEA, cocamide DEA, dodecyldimethylamine oxide, block copolymers of polyethylene glycol and polypropylene glycol (poloxamers), block copolymers of polyethylene glycol and polypropylene oxide (for instance Pluronic surfactants), polyvinyl pyrrolidone K25, polyvinyl alcohol, oligolactic acid, sodium dioctyl sulfosuccinate and polyethoxylated tallow amine (POEA).

Preferably, the one or more surfactants comprise a polysorbate and/or a sorbitan alkyl ester. The one or more surfactants may for instance comprise polysorbate 20 (polyoxyethylene (20) sorbitan monolaurate), polysorbate 40 (polyoxyethylene (20) sorbitan monopalmitate), polysorbate 60 (polyoxyethylene (20) sorbitan monostearate) or polysorbate 80 (polyoxyethylene (20) sorbitan monooleate). The one or more surfactants may for instance comprise sorbitan monolaurate (Span 20), sorbitan monooleate (Span 80) or sorbitan trioleate (Span 85). Preferably, the sterile liquid vehicle comprises polysorbate 20 and/or sorbitan monolaurate (Span 20).

For instance, the method may comprise administering to the patient an inhalable liquid pharmaceutical composition comprising:

- water;
- particles consisting of ensifentrine free base at a concentration of from 0.1 to 20 mg/mL;
- one or more tonicity adjusters at a total concentration of from 1.0 to 15 mg/mL;
- one or more buffers at a total concentration of from 0.1 to 4 mg/mL; and
- one or more surfactants at a total concentration of from 0.05 to 3 mg/mL.

The inhalable liquid pharmaceutical composition may comprise:

- water;
- particles consisting of ensifentrine free base at a concentration of from 0.5 to 6 mg/mL;
- sodium chloride at a concentration of from 5 to 12 mg/mL;
- sodium dihydrogen phosphate dihydrate at a concentration of from 0.3 to 2 mg/mL;
- disodium phosphate dihydrate at a concentration of from 0.3 to 2 mg/mL;
- polysorbate 20 at a concentration of from 0.1 to 1.5 mg/mL; and
- sorbitan monolaurate at a concentration of from 0.01 to 0.5 mg/mL.

The compound may be used in combination with a second active agent. The compound may be administered separately or simultaneously with the second active agent. The patient may already be taking a second active agent as a background therapy for COPD. Alternatively, treatment with the second active agent may start at around the same time as treatment with the compound. The compound and the second active agent may be administered in a fixed combination.

The second active agent is typically a muscarinic receptor antagonist, a beta-adrenergic receptor agonist or an inhaled corticosteroid. The compound may accordingly be used in combination with muscarinic receptor antagonist, a beta-adrenergic receptor agonist or an inhaled corticosteroid. The second active agent may be a long-acting muscarinic receptor antagonist (LAMA) or a long-acting beta-adrenergic receptor agonist (LABA).

Examples of LAMAs include aclidinium, darotropium, tiotropium, glycopyrrolate and umeclidinium. Examples of LABAs include salmeterol, formoterol, indacaterol, vilanterol, olodaterol, abediterol and carmoterol. Examples of inhaled corticosteroids include beclomethosone, budesonide, fluticasone propionate, ciclesonide, mometasone and fluticasone furoate.

The patient may be using a beta-agonist (for instance salbutamol) as a rescue medication.

The invention is described in more detail by the following Example.

EXAMPLES

Study design

A clinical study was conducted to determine the efficacy of ensifentrine in treating COPD compared with placebo. Ensifentrine was administered by nebuliser at a dose of 3 mg twice daily (BID) for 24 weeks. The study was a multi-centre, randomized, double-blind, parallel-group, placebo-controlled trial with around 800 patients and 5:3 randomization.

The study population included patients aged 40-80 years with moderate to severe COPD (FEV_1 30% – 70% p.n., FEV_1/forced vital capacity (FVC) ratio < 0.7, with mMRC ≥ 2). The randomization stratified (a) the use of stable background maintenance LAMA or LABA therapy use (approx. 50%. yes or no) and (b) cigarette smoking (current or former). Inhaled corticosteroid (ICS) maintenance therapy was permitted in up to 20% of patients under certain provisions.

The primary endpoint of the study was change from baseline in average FEV_1 area under the curve (AUC)0-12h post-dose at week 12. Secondary endpoints of the study included: peak FEV_1 over 4 hours post-dose at Week 12; morning trough FEV_1 at Week 12; and other endpoints including moderate/severe COPD exacerbations frequency over 24 Weeks.

Methods

COPD severity is derived as follows: mild: 80%<=FEV_1, moderate: 50%<=FEV_1<80% predicted, severe: 30%<=FEV_1<50% predicted and very severe: FEV_1<30% predicted, post bronchodilator dose at Screening.

Baseline FEV_1 is the mean of the two measurements taken before study medication on the day of first dosing, i.e. ≤ 40 minutes and just prior to dosing, both pre-dose on day 1.

Average FEV_1 AUC0-12h is defined as area under the curve over 12 hours of the FEV_1, divided by 12 hours.

Formulation

The investigational product and placebo were provided in 2.5 mL unit dose format in an ampule and administered via a nebuliser. The formulation of the investigational product (ensifentrine suspension formulation) and placebo are shown in Table 1 below.

Constituent	Concentration (mg/mL)
Ensifentrine particles (RPL554)	1.2 (for the active) or 0 (for Placebo)
Polysorbate 20 (Tween 20)	0.50
Sorbitan Monolaurate (Span 20)	0.05
Sodium Dihydrogen Phosphate Dihydrate	0.744
Disodium Hydrogen Phosphate Dihydrate	0.853
Sodium Chloride	8.60
Water	q.s. to 1 mL

Table 1

Results

The primary endpoint of average FEV_1 (AUC)0-12h at Week 12 was met. All subgroups showed improvement in lung function with ensifentrine that was statistically significant. The results are shown in Table 2 and Figure 1.

Average FEV_1 (AUC)0-12h post-dose at Week 12: Change from Baseline (CFB)	***Ensifentrine 3 mg*** *(n = 498)*	***Placebo*** *(n = 291)*
Observed N	424	231
Mean Baseline FEV_1, L	1.3323	1.2316
CFB Least Squares Mean, mL (95% CI)	48.2 (30.0, 66.5)	-45.7 (-69.7, -21.6)
Placebo-corrected CFB LS Mean Diff., mL (95% CI)	93.9 (64.5, 123.3)	-
p-value	<0.0001	-

Table 2

The average mL change in baseline for FEV_1 (AUC)0-12h at Week 12 for patients with moderate and severe COPD respectively is shown in Table 3 below.

COPD type	Average change in baseline FEV_1 (AUC)0-12h at Week 12
Moderate	139 mL
Severe	45 mL

Table 3

Significant increases in FEV_1 were observed for both moderate and severe COPD. However, a particularly notable increase was observed in the treatment of patients with moderate COPD.

Conclusion

It has been found that ensifentrine provides a statistically significant improvement in lung function in all subgroups of COPD patients in the study. In addition, ensifentrine has been found to be particularly effective in improving lung function in moderate COPD.

CLAIMS

1. A compound for use in a method of treating moderate COPD in a patient, which compound is ensifentrine or a pharmaceutically acceptable salt thereof.

2. A compound for use according to claim 1, wherein the method comprises administering the compound to the patient by inhalation.

3. A compound for use according to claim 1 or claim 2, wherein the method comprises administering the compound to the patient by inhalation by nebuliser.

4. A compound for use according to any one of the preceding claims, wherein the compound is ensifentrine.

5. A compound for use according to any one of the preceding claims, wherein the method comprises administering the compound to the patient once, twice or three times per day.

6. A compound for use according to any one of the preceding claims, wherein the method comprises administering the compound to the patient twice a day.

7. A compound for use according to any one of the preceding claims, wherein the method comprises administering a total daily dose of the compound of from 0.5 to 10 mg, preferably from 5 to 7 mg.

8. A compound for use according to any one of the preceding claims, wherein the method comprises administering the compound to the patient twice a day in a first dose of from 2 to 4 mg and a second dose of from 2 to 4 mg.

9. A compound for use according to any one of the preceding claims, wherein the method comprises administering a dose of about 3 mg the compound to the patient twice a day (3 mg BID), preferably wherein the method comprises

administering by nebuliser a dose of about 3 mg the compound to the patient twice a day.

10. A compound for use according to any one of the preceding claims, wherein the method comprises administering the compound to the patient at least once per day for at least 8 weeks, preferably for at least 16 weeks, more preferably for at least 24 weeks.

11. A compound for use according to any one of the preceding claims, wherein the patient has been determined to have moderate COPD by measuring $FEV_1/FVC < 0.7$ and $50\ \% \leq FEV_1 < 80\ \%$ predicted FEV_1 value, where FEV_1 is forced expiratory volume in 1 second and FVC is forced vital capacity as measured between 15 and 30 minutes after a dose of a bronchodilator, optionally wherein the bronchodilator is salbutamol.

12. A compound for use according to any one of the preceding claims, wherein the method comprising administering an inhalable pharmaceutical composition comprising a suspension of particles of the compound in a diluent.

13. A compound for use according to any one of the preceding claims, wherein the compound is used in combination with a muscarinic receptor antagonist, a beta-adrenergic receptor agonist or an inhaled corticosteroid.

14. A method of treating moderate COPD in a patient, which method comprises administering a therapeutically effective amount of a compound which is ensifentrine or a pharmaceutically acceptable salt thereof to the patient.

15. Use of a compound which is ensifentrine or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating moderate COPD.

16. A suspension formulation having the composition:

Constituent	**Concentration (mg/mL)**
Ensifentrine particles (RPL554)	1.2
Polysorbate 20 (Tween 20)	0.50
Sorbitan Monolaurate (Span 20)	0.05
Sodium Dihydrogen Phosphate Dihydrate	0.744
Disodium Hydrogen Phosphate Dihydrate	0.853
Sodium Chloride	8.60
Water	q.s. to 1 mL

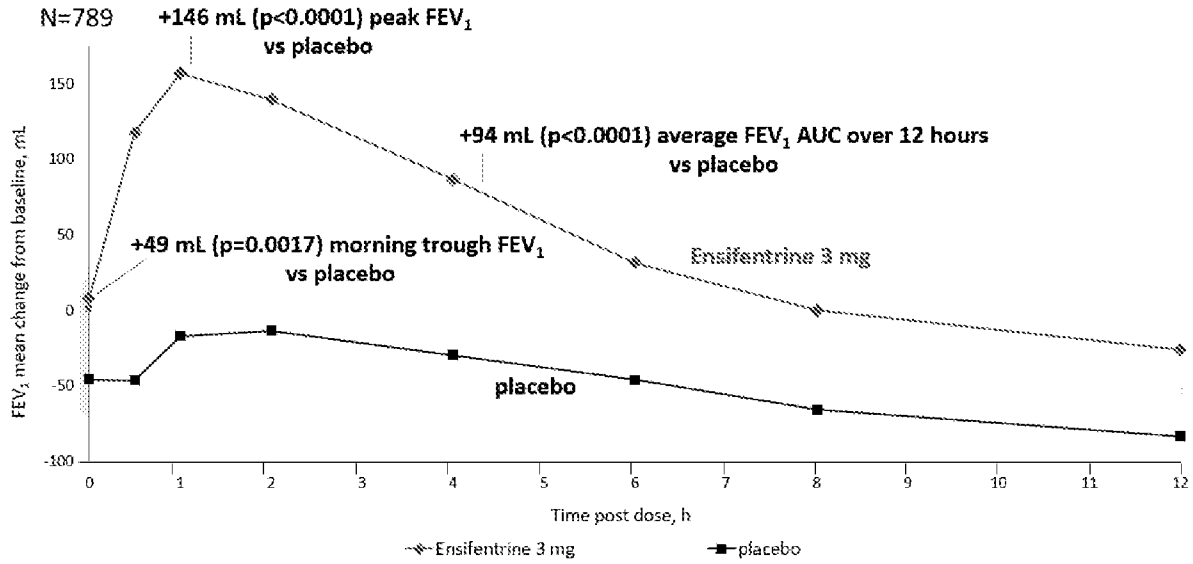

N=789
+146 mL (p<0.0001) peak FEV1 vs placebo
+94 mL (p<0.0001) average FEV1 AUC over 12 hours vs placebo
+49 mL (p=0.0017) morning trough FEV1 vs placebo
Ensifentrine 3 mg
placebo
FEV1 mean change from baseline, mL
150
100
50
0
-50
-100
0
1
2
3
4
5
6
7
8
9
10
11
12
Time post dose, h
Ensifentrine 3 mg
placebo

FIGURE 1

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2023/052082

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/519 A61K9/12 A61K9/00 A61K47/02 A61K47/26
A61P11/08
ADD.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, BIOSIS, CHEM ABS Data, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	MARIO CAZZOLA ET AL: "Ensifentrine (RPL554): an inhaled 'bifunctional' dual PDE3/4 inhibitor for the treatment of asthma and chronic obstructive pulmonary disease", PHARMACEUTICAL PATENT ANALYST, vol. 7, no. 6, 1 November 2018 (2018-11-01), pages 249-257, XP055651020, GB ISSN: 2046-8954, DOI: 10.4155/ppa-2018-0030	1-11, 13-16
Y	page 253, paragraph 4 - paragraph 6 the whole document	12,16

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"Y" document of particular relevance;; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

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Date of the actual completion of the international search	Date of mailing of the international search report
13 October 2023	20/10/2023

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Langer, Oliver

5

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