of the etiology, hypoxemia induced by bronchoconstriction and inflammation associated with asthma exacerbations will contribute to a cycle of sickling and subsequent complications of SCD. Recent studies confirm that asthma predisposes to complications of SCD such as pain crises, acute chest syndrome, and stroke, and is associated with increased mortality.

[0015] Chronic obstructive pulmonary disease (COPD) is the fourth leading cause of death in the United States, accounting for more than 110,000 deaths per year. COPD encompasses both chronic bronchitis and emphysema and is characterized by airway narrowing, air trapping, alveolar destruction, and excessive airway inflammation and oxidative stress. Cigarette smoke (CS) is the most common cause of COPD. In COPD there are marked increases in both inflammation and oxidative stress, which can be replicated in mice by exposing them to tobacco smoke.

[0016] Presently, there exist numerous regimens for the treatment of lung diseases and disorders, including short-acting bronchodilators (i.e. short-acting beta agonists), long-acting bronchodilators (i.e. long-acting beta agonists), phosphodiesterase-4 ("PDE4") inhibitors, corticosteroids, leukotriene receptor antagonists, expectorants and methylxanthines. However, such drugs are not always effective at reducing the symptoms, slowing the progression, or reversing the course of the clinical manifestation of the condition. Additionally, current regimens are limited in dose strength due to side effects and by inefficient delivery to a subject's lungs.

SUMMARY

[0017] The present disclosure ~~provides~~ describes compositions comprising fatty acid agents including, for example, 15-HEPE (also referred to as "15-OHEPA") used singly, in combination and/or in combination with a second active agent for treatment of lung diseases or disorders, such as asthma or COPD.

[0018] The present disclosure also describes ~~provides~~ methods for treating a lung disease or disorder mediated by 15-HEPE in a subject in need thereof comprising administering to subject a pharmaceutical composition comprising a therapeutically effective amount of 15-HEPE or combinations thereof. In some ~~embodiments~~examples, the pharmaceutical composition

comprises about 5 µg to about 10,000 mg of 15-HEPE, for example about 50 µg to about 4,000 mg of 15-HEPE. In some embodiments, the method comprises orally administering about 50 mg to about 4,000 mg of 15-HEPE to the subject per day.

[0019] The present disclosure also describes ~~provides~~ methods for treating a lung disease or disorder mediated by 15-HEPE in a subject in need thereof comprising administering to a subject a pharmaceutical composition comprising a therapeutically effective amount of 15-HEPE. In some ~~embodiments~~examples, the pharmaceutical composition comprises about 5 µg to about 10,000 mg of 15-HEPE, for example about 50 µg to about 4,000 mg of 15-HEPE. In some ~~embodiments~~examples, the method comprises administering about 50 mg to about 4,000 mg of 15-HEPE to the subject per day.

[0020] In some examples~~embodiments~~, the pharmaceutical composition comprises one or more pharmaceutically acceptable excipients.

[0021] In some examples~~embodiments~~, the pharmaceutical composition comprises a second active agent. In some examples~~embodiments~~, the second active agent is one or more of: short-acting bronchodilators (i.e. short-acting beta agonists), long-acting bronchodilators (i.e. long-acting beta agonists), phosphodiesterase-4 ("PDE4") inhibitors, corticosteroids, leukotriene receptor antagonists, expectorants and methylxanthines.

[0022] In some examples~~embodiments~~, the step of administering comprises delivering the pharmaceutical composition to a lung of the subject by dry-powder inhaler. In some examples~~embodiments~~, the pharmaceutical composition is in dry powder form.

[0023] In some examples~~embodiments~~, the step of administering comprises delivering the pharmaceutical composition to a lung of the subject by metered dose inhaler. In some examples~~embodiments~~, the pharmaceutical composition is in powder form. In some examples~~embodiments~~, the pharmaceutical composition further comprises a propellant.

[0024] In some examples~~embodiments~~, the step of administering comprises delivering the pharmaceutical composition to a lung of the subject by nebulizer. In some examples~~embodiments~~, the pharmaceutical composition is a solution comprising a solvent system. In some examples~~embodiments~~, the solvent system comprises an alcohol and/or a polyol. In some

examplesembodiments, the solvent system does not include an alcohol or a polyol. In some examplesembodiments, the pharmaceutical composition is a suspension.

[0025] In some examplesembodiments, the step of administering the pharmaceutical composition comprises on oral dosage form. In some examplesembodiments, compositions of the invention are in the form of solid dosage forms. Non-limiting examples of suitable solid dosage forms include tablets (e.g. suspension tablets, bite suspension tablets, rapid dispersion tablets, chewable tablets, melt tablets, effervescent tablets, bilayer tablets, etc), caplets, capsules (e.g. a soft or a hard gelatin capsule filled with solid and/or liquids), powder (e.g. a packaged powder, a dispensable powder or an effervescent powder), lozenges, sachets, cachets, troches, pellets, granules, microgranules, encapsulated microgranules, powder aerosol formulations, or any other solid dosage form reasonably adapted for oral administration.

[0026] In some examplesembodiments, the pharmaceutical composition is formulated for intravenous or intramuscular injection by methods known in the art.

[0027] In some examplesembodiments, the method comprises co-administering a pharmaceutical composition comprising 15-HEPE with a second active agent. In some examplesembodiments, the second active agent is co-formulated with the pharmaceutical composition. In some examplesembodiments, the second active agent is administered simultaneously, concomitantly, or within 1 to 24 hours of the pharmaceutical composition comprising 15-HEPE.

[0028] In one exampleembodiment, the 15-HEPE is in the form of an ester. In another embodiment, the compositions comprise a $C_1 - C_5$ alkyl ester of 15-HEPE. In another exampleembodiment, the compositions comprise a methyl ester, propyl ester, or butyl ester. In another example embodiment the 15-HEPE is in the form of a pharmaceutically acceptable salt.

[0029] In another exampleembodiment, the 15-HEPE comprises lithium, mono, di- or triglyceride or any other ester or 15-HEPE. In another exampleembodiment, the 15-HEPE comprises salts, including but not limited to sodium, lysine, ornithine, piperazine or meglumine. In yet another exampleembodiment, the 15-HEPE the free acid form of 15-HEPE.

[0030] In one example~~embodiment~~, 15-HEPE present in a composition of the invention comprises at least 90% by weight 15-HEPE (as the term "15-HEPE" is defined and exemplified herein). 15-HEPE compositions can comprise even higher purity compositions, for example at least 95% by weight 15-HEPE or at least 97% by weight 15-HEPE, wherein the 15-HEPE is any form of 15-HEPE as set forth herein.

[0031] In another example~~embodiment~~, 15-HEPE is present in a composition of the invention in an amount of about 5 µg to about 10,000 mg, about 25 mg to about 7500mg, 50 mg to about 5000 mg, about 75 mg to about 2500 mg, about 100 mg to about 1000 mg, or about 50 µg to about 1000 µg, for example about 5 µg, about 10 µg, about 15 µg, about 20 µg, about 25 µg, about 30 µg, about 35 µg, about 40 µg, about 45 µg, about 50 µg, about 55 µg, about 60 µg, about 65 µg, about 70 µg, about 75 µg, about 80 µg, about 85 µg, about 90 µg, about 95 µg, about 100 µg, about 105 µg, about 110 µg, about 115 µg, about 120 µg, about 125 µg, about 130 µg, about 135 µg, about 140 µg, about 145 µg, about 150 µg, about 155 µg, about 160 µg, about 165 µg, about 170 µg, about 175 µg, about 180 µg, about 185 µg, about 190 µg, about 195 µg, about 200 µg, about 205 µg, about 210 µg, about 215 µg, about 220 µg, about 225 µg, about 230 µg, about 235 µg, about 240 µg, about 245 µg, about 250 µg, about 255 µg, about 260 µg, about 265 µg, about 270 µg, about 275 µg, about 280 µg, about 285 µg, about 290 µg, about 295 µg, about 300 µg, about 305 µg, about 310 µg, about 315 µg, about 320 µg, about 325 µg, about 330 µg, about 335 µg, about 340 µg, about 345 µg, about 350 µg, about 355 µg, about 360 µg, about 365 µg, about 370 µg, about 375 µg, about 380 µg, about 385 µg, about 390 µg, about 395 µg, about 400 µg, about 405 µg, about 410 µg, about 415 µg, about 420 µg, about 425 µg, about 430 µg, about 435 µg, about 440 µg, about 445 µg, about 450 µg, about 455 µg, about 460 µg, about 465 µg, about 470 µg, about 475 µg, about 480 µg, about 485 µg, about 490 µg, about 495 µg, about 500 µg, about 505 µg, about 510 µg, about 515 µg, about 520 µg, about 525 µg, about 530 µg, about 535 µg, about 540 µg, about 545 µg, about 550 µg, about 555 µg, about 560 µg, about 565 µg, about 570 µg, about 575 µg, about 580 µg, about 585 µg, about 590 µg, about 595 µg, about 600 µg, about 605 µg, about 610 µg, about 615 µg, about 620 µg, about 625 µg, about 630 µg, about 635 µg, about 640 µg, about 645 µg, about 650 µg, about 655 µg, about 660 µg,

mg, about 6825 mg, about 6850 mg, about 6875 mg, about 6900 mg, about 6925 mg, about 6950 mg, about 6975 mg, about 7000 mg, about 7025 mg, about 7050 mg, about 7075 mg, about 7100 mg, about 7125 mg, about 7150 mg, about 7175 mg, about 7200 mg, about 7225 mg, about 7250 mg, about 7275 mg, about 7300 mg, about 7325 mg, about 7350 mg, about 7375 mg, about 7400 mg, about 7425 mg, about 7450 mg, about 7475 mg, about 7500 mg, about 7525 mg, about 7550 mg, about 7575 mg, about 7600 mg, about 7625 mg, about 7650 mg, about 7675 mg, about 7700 mg, about 7725 mg, about 7750 mg, about 7775 mg, about 7800 mg, about 7825 mg, about 7850 mg, about 7875 mg, about 7900 mg, about 7925 mg, about 7950 mg, about 7975 mg, about 8000 mg, about 8025 mg, about 8050 mg, about 8075 mg, about 8100 mg, about 8125 mg, about 8150 mg, about 8175 mg, about 8200 mg, about 8225 mg, about 8250 mg, about 8275 mg, about 8300 mg, about 8325 mg, about 8350 mg, about 8375 mg, about 8400 mg, about 8425 mg, about 8450 mg, about 8475 mg, about 8500 mg, about 8525 mg, about 8550 mg, about 8575 mg, about 8600 mg, about 8625 mg, about 8650 mg, about 8675 mg, about 8700 mg, about 8725 mg, about 8750 mg, about 8775 mg, about 8800 mg, about 8825 mg, about 8850 mg, about 8875 mg, about 8900 mg, about 8925 mg, about 8950 mg, about 8975 mg, about 9000 mg, about 9025 mg, about 9050 mg, about 9075 mg, about 9100 mg, about 9125 mg, about 9150 mg, about 9175 mg, about 9200 mg, about 9225 mg, about 9250 mg, about 9275 mg, about 9300 mg, about 9325 mg, about 9350 mg, about 9375 mg, about 9400 mg, about 9425 mg, about 9450 mg, about 9475 mg, about 9500 mg, about 9525 mg, about 9550 mg, about 9575 mg, about 9600 mg, about 9625 mg, about 9650 mg, about 9675 mg, about 9700 mg, about 9725 mg, about 9750 mg, about 9775 mg, about 9800 mg, about 9825 mg, about 9850 mg, about 9875 mg, about 9900 mg, about 9925 mg, about 9950 mg, about 9975 mg, or about 10,000 mg.

[0032] In one example~~embodiment~~, a composition of the invention contains not more than about 10%, not more than about 9%, not more than about 8%, not more than about 7%, not more than about 6%, not more than about 5%, not more than about 4%, not more than about 3%, not more than about 2%, not more than about 1%, or not more than about 0.5%,

by weight of other omega-3 fatty acids such eicosapentaenoic acid, alpha linolenic acid, docosahexaenoic acid, docosapentaenoic acid or derivatives thereof.

[0033] In another example~~embodiment~~, 15-HEPE represents at least about 60%, at least about 70%, at least about 80%, at least about 90%, at least about 95%, at least about 97%, at least about 98%, at least about 99%, or 100%, by weight, of all fatty acids present in a composition of the invention.

[0034] In one example~~embodiment~~, the present disclosure provides a method for treating a lung disease or disorder comprising administering a pharmaceutical composition comprising 15-HEPE to a subject in need thereof.

[0035] These and other example~~embodiments~~ of the invention are described in further detail below.

BRIEF DESCRIPTION OF THE DRAWINGS

[0036] FIG. 1 shows ventilatory pressure (mm Hg) changes following exposition of nebulized histamine doses after seven consecutive days of gavage with vehicle.

[0037] FIG. 2 shows ventilatory pressure (mm Hg) changes following exposition of nebulized histamine doses after seven consecutive days of gavage with bambuterol at 0.27 mg/kg/day.

[0038] FIG. 3 shows ventilatory pressure (mm Hg) changes following exposition of nebulized histamine doses after seven consecutive days of gavage with 15-HEPE at 50 mg/kg/day.

[0039] FIG. 4 shows ventilatory pressure (mm Hg) changes following exposition of nebulized histamine doses after seven consecutive days of gavage with 15-HEPE at 500 mg/kg/day.

[0040] FIG. 5 shows ventilatory pressure (mm Hg) changes following exposition of nebulized histamine doses after seven consecutive days of gavage with vehicle, bambuterol (0.27mg/kg/day),OH-EPA (50 mg/kg/day) and OH-EPA (500mg/kg/day).

CLAIMS

1. Use of 100 mg to about 1000 mg of 15-HEPE free acid in the manufacture of a medicament for treating chronic obstructive pulmonary disease (COPD) by daily administration.

2. The use of claim 1, wherein the 100 mg to about 1000 mg of 15-HEPE free acid is present in a dosage unit of the medicament.

3. The use of claim 2, wherein the dosage unit comprises a capsule.

4. The use of claim 1, wherein the 15-HEPE free acid comprises at least about 90% by weight of the medicament.

5. The use of claim 1, wherein the 15-HEPE free acid comprises at least about 95% by weight of the medicament.

6. The use of claim 1, wherein the medicament comprises 400 mg to about 700 mg of 15-HEPE free acid.

7. The use of claim 6, wherein the 400 mg to about 700 mg of 15-HEPE free acid is present in a dosage unit of the medicament.

8. The use of claim 7, wherein the dosage unit comprises a capsule.

9. The use of claim 6, wherein the 15-HEPE free acid comprises at least about 90% by weight of the medicament.

10. The use of claim 6, wherein the 15-HEPE free acid comprises at least about 95% by weight of the medicament.

CLAIMS

I/We claim:

1. A method for treating a lung disease or disorder comprising administering a pharmaceutical composition comprising 15-HEPE to a subject in need thereof.

2. The method of claim 1, wherein the pharmaceutical composition comprises about 50 µg to about 4,000 mg of 15-HEPE.

3. The method of claim 1 or 2, wherein the subject is administered an amount of the composition sufficient to provide about 1 to about 2,000 mg of 15-HEPE to the subject per day.

4. A method for treating a disease or disorder comprising administering a pharmaceutical composition comprising 15-HEPE to a lung of a subject in need thereof.

5. The method of claim 4, wherein the pharmaceutical composition comprises about 50 µg to about 1,000 µg/mL of 15-HEPE.

6. The method of claim 4 or 5, wherein the subject is administered an amount of the composition sufficient to provide about 5 µg to about 1,000 µg of 15-HEPE to the subject per day.

7. The method of any of claims 1 to 6, wherein the disease or disorder is selected from the group consisting of: asthma and COPD.

8. The method of any of claims 1 to 7, wherein the pharmaceutical composition further comprises a second active agent.

9. The method of claim 8, wherein the second active agent is selected from the group consisting of: short-acting bronchodilators, long-acting bronchodilators,

phosphodiesterase-4 inhibitors, corticosteroids, leukotriene receptor antagonists, expectorants and methylxanthines.