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(54) **Title:** VISMODEGIB AND PIRFENIDONE COMBINATION THERAPY

(57) **Abstract:** The present invention relates to methods of administering both vismodegib and pirfenidone to patients in need thereof.



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VISMODEGIB AND PIRFENIDONE COMBINATION THERAPY**CROSS REFERENCE TO RELATED APPLICATION**

[0001] This application claims the benefit of and priority under 35 USC § 119 to United States Provisional Application Number 62/266,252, filed December 11, 2015, the contents of which are incorporated by reference in its entirety.

BACKGROUND

[0002] Pirfenidone is a small molecule with a molecular weight of 185.23 Daltons whose chemical name is 5-methyl-1-phenyl-2-(1H)-pyridone. Pirfenidone has anti-fibrotic properties and has been investigated for therapeutic benefits to patients suffering from various fibrotic conditions. It is approved for treatment of idiopathic pulmonary fibrosis (IPF) in several countries.

[0003] Vismodegib is a small molecule with a molecular weight of 421.30 Daltons whose chemical name is 2-chloro-N-(4-chloro-3-pyridin-2-ylphenyl)-4-methylsulfonylbenzamide. Vismodegib is a hedgehog pathway inhibitor indicated for the treatment of adults with metastatic basal cell carcinoma, or with locally advanced basal cell carcinoma that has recurred following surgery or who are not candidates for surgery, and who are not candidates for radiation. It is approved in Europe, Canada, and the United States for treatment of basal cell carcinoma under the trade name Erivedge®. Vismodegib is not approved for the treatment of IPF.

SUMMARY

[0004] Provided herein are methods comprising administering to a patient (i) vismodegib in a total daily amount of about 100 mg/day to about 200 mg/day; and (ii) pirfenidone optionally with food, in a total daily amount of at least 1600 mg/day to about 3000 mg/day. The food can be a meal. In some cases, the pirfenidone is administered at about 1800 mg/day. In various cases, the pirfenidone is administered at about 2300 mg/day to about 2500 mg/day, or about 2400 mg/day or 2403 mg/day. The pirfenidone can be administered in two or three divided doses. The pirfenidone can be administered as a capsule. The pirfenidone can be administered as a tablet. The pirfenidone can be administered at the same time as or within 30 minutes after a meal. The vismodegib can be administered as a capsule. The vismodegib can be administered under fasted conditions. The vismodegib can be administered with food. In some cases, the vismodegib is administered at about 145 mg/day to 155 mg/day. In some cases, the vismodegib is administered at about 150 mg/day. In some cases, the vismodegib is administered as a single dose. In some cases, the methods further

comprise administering pirfenidone, in a total daily amount at least 1600 mg/day to about 3000 mg/day for four weeks prior to administering vismodegib and pirfenidone. In some cases, the patient was treated with pirfenidone, in a total daily amount at least 1600 mg/day to about 3000 mg/day for at least twenty-four weeks prior to the administration of vismodegib.

[0005] In the methods disclosed herein, the patient can suffer from idiopathic pulmonary fibrosis, pulmonary fibrosis, bronchiolitis obliterans, chronic lung transplant rejection, scleroderma, primary focal segmental glomerulosclerosis (FSGC) or membranoproliferative glomerulonephritis (MPGN), idiopathic interstitial pneumonia, interstitial lung disease in systemic sclerosis, a fibrosis condition of the lung, autoimmune lung diseases, benign prostate hypertrophy, coronary or myocardial infarction, atrial fibrillation, cerebral infarction, myocardial fibrosis, musculoskeletal fibrosis, post-surgical adhesions, liver cirrhosis, renal fibrotic disease, fibrotic vascular disease, scleroderma, Hermansky-Pudlak syndrome, neurofibromatosis, Alzheimer's disease, diabetic retinopathy, or skin lesions, lymph node fibrosis associated with HIV, chronic obstructive pulmonary disease (COPD), inflammatory pulmonary fibrosis, rheumatoid arthritis; rheumatoid spondylitis; osteoarthritis; gout, other arthritic conditions; sepsis; septic shock; endotoxic shock; gram-negative sepsis; toxic shock syndrome; myofascial pain syndrome (MPS); Shigellosis; asthma; adult respiratory distress syndrome; inflammatory bowel disease; Crohn's disease; psoriasis; eczema; ulcerative colitis; glomerular nephritis; scleroderma; chronic thyroiditis; Grave's disease; Ormond's disease; autoimmune gastritis; myasthenia gravis; autoimmune hemolytic anemia; autoimmune neutropenia; thrombocytopenia; pancreatic fibrosis; chronic active hepatitis including hepatic fibrosis; acute or chronic renal disease; renal fibrosis; diabetic nephropathy; irritable bowel syndrome; pyresis; restenosis; cerebral malaria; stroke or ischemic injury; neural trauma; Alzheimer's disease; Huntington's disease; Parkinson's disease; acute or chronic pain; allergies, including allergic rhinitis or allergic conjunctivitis; cardiac hypertrophy, chronic heart failure; acute coronary syndrome; cachexia; malaria; leprosy; leishmaniasis; Lyme disease; Reiter's syndrome; acute synovitis; muscle degeneration, bursitis; tendonitis; tenosynovitis; herniated, ruptured, or prolapsed intervertebral disk syndrome; osteopetrosis; thrombosis; silicosis; pulmonary sarcosis; bone resorption diseases, such as osteoporosis or multiple myeloma-related bone disorders; cancer, including but not limited to metastatic breast carcinoma, colorectal carcinoma, malignant melanoma, gastric cancer, or non-small cell lung cancer; graft-versus-host reaction; or auto-immune diseases, such as multiple sclerosis, lupus or fibromyalgia; AIDS or other viral diseases such as Herpes Zoster, Herpes Simplex I or II, influenza virus, Severe Acute Respiratory Syndrome (SARS) or

cytomegalovirus; or diabetes mellitus, proliferative disorders (including both benign or malignant hyperplasias), acute myelogenous leukemia, chronic myelogenous leukemia, Kaposi's sarcoma, metastatic melanoma, multiple myeloma, breast cancer, including metastatic breast carcinoma; colorectal carcinoma; malignant melanoma; gastric cancer; non-small cell lung cancer (NSCLC); bone metastases; pain disorders including neuromuscular pain, headache, cancer pain, dental pain, or arthritis pain; angiogenic disorders including solid tumor angiogenesis, ocular neovascularization, or infantile hemangioma; conditions associated with the cyclooxygenase or lipoxygenase signaling pathways, including conditions associated with prostaglandin endoperoxide synthase-2 (including edema, fever, analgesia, or pain); organ hypoxia; thrombin-induced platelet aggregation; or protozoal diseases. In various cases, the patient suffers from a fibrotic condition. In some cases, the patient suffers from IPF.

[0006] For the methods disclosed herein, the patient can exhibit a percent of predicted forced vital capacity volume (%FVC) of about 90% or less prior to starting therapy. In some cases, the %FVC is about 80% or less, or about 50% to about 80%. In various cases, the patient exhibits a ratio of forced expiratory volume in one second (FEV1) to forced vital capacity volume (FVC) of about 0.70 or greater, about 0.75 or greater, or about 0.80 or greater, prior to starting therapy. In some cases, the patient has been diagnosed with pulmonary fibrosis, optionally IPF, for at least six months, and optionally less than 48 months, prior to starting therapy. In various cases, the patient exhibits a diffusion capacity (%DLco) ranging from about 30% to about 90%, prior to starting therapy.

DETAILED DESCRIPTION

[0007] In the combination methods disclosed herein, vismodegib can be delivered, for example, via oral or intrapulmonary administration, and pirfenidone can be delivered, for example, via oral or intrapulmonary administration. In some embodiments, vismodegib can be delivered via oral administration and pirfenidone can be delivered via oral or intrapulmonary administration. In some embodiments, vismodegib can be delivered via oral administration and pirfenidone can be delivered via oral administration.

Combination Methods

[0008] The methods disclosed herein provide administering to a patient a combination of pirfenidone and vismodegib. In some embodiments, the vismodegib and pirfenidone are administered via different routes of administration, e.g. pirfenidone via intrapulmonary administration and vismodegib via oral administration.

[0009] In some embodiments, the pirfenidone is administered with food, such as a meal. The vismodegib can be administered under fasted conditions, or with food.

[0010] In various embodiments, the methods provided herein result in an increased therapeutic or safety benefit for the patient, compared to administration to a patient receiving pirfenidone and vismodegib not according to the provided methods. In some cases, the methods provide an increased therapeutic benefit. Measurement of therapeutic benefit can be a clinical end point. For example, % forced vital capacity (FVC), a ratio of forced expiratory volume in one second (FEV1) to forced vital capacity volume (FVC) (FEV1/FVC), or survival rate are clinical end points often assessed in IPF clinical studies. As will be readily appreciated, other clinical end points for other diseases can be used to assess increased therapeutic benefit. Measurement of safety benefit can be incidence of one or more adverse events.

[0011] In some embodiments, the combination of pirfenidone and vismodegib may be used to treat a patient. The patient may be suffering from any disease or condition for which pirfenidone therapy may be useful in ameliorating symptoms. For example, the patient suffers from a fibrotic disorder, such as a fibrotic disorder of the lung, kidney, liver, heart, or other organ; an inflammatory disease; an autoimmune disease; or fibrosis accompanying tissue injury from, e.g., infarction, infection, cancer, cirrhosis, and the like. Pirfenidone is known to possess both anti-fibrotic and anti-inflammatory activities. For example, the patient suffers from idiopathic pulmonary fibrosis, pulmonary fibrosis, bronchiolitis obliterans, chronic lung transplant rejection, scleroderma, primary focal segmental glomerulosclerosis (FSGC) or membranoproliferative glomerulonephritis (MPGN), idiopathic interstitial pneumonia, interstitial lung disease in systemic sclerosis, a fibrosis condition of the lung, autoimmune lung diseases, benign prostate hypertrophy, coronary or myocardial infarction, atrial fibrillation, cerebral infarction, myocardial fibrosis, musculoskeletal fibrosis, post-surgical adhesions, liver cirrhosis, renal fibrotic disease, fibrotic vascular disease, scleroderma, Hermansky-Pudlak syndrome, neurofibromatosis, Alzheimer's disease, diabetic retinopathy, or skin lesions, lymph node fibrosis associated with HIV, chronic obstructive pulmonary disease (COPD), inflammatory pulmonary fibrosis, rheumatoid arthritis; rheumatoid spondylitis; osteoarthritis; gout, other arthritic conditions; sepsis; septic shock; endotoxic shock; gram-negative sepsis; toxic shock syndrome; myofascial pain syndrome (MPS); Shigellosis; asthma; adult respiratory distress syndrome; inflammatory bowel disease; Crohn's disease; psoriasis; eczema; ulcerative colitis; glomerular nephritis; scleroderma; chronic thyroiditis; Grave's disease; Ormond's disease; autoimmune gastritis; myasthenia

gravis; autoimmune hemolytic anemia; autoimmune neutropenia; thrombocytopenia; pancreatic fibrosis; chronic active hepatitis including hepatic fibrosis; acute or chronic renal disease; renal fibrosis; diabetic nephropathy; irritable bowel syndrome; pyresis; restenosis; cerebral malaria; stroke or ischemic injury; neural trauma; Alzheimer's disease; Huntington's disease; Parkinson's disease; acute or chronic pain; allergies, including allergic rhinitis or allergic conjunctivitis; cardiac hypertrophy, chronic heart failure; acute coronary syndrome; cachexia; malaria; leprosy; leishmaniasis; Lyme disease; Reiter's syndrome; acute synovitis; muscle degeneration, bursitis; tendonitis; tenosynovitis; herniated, ruptured, or prolapsed intervertebral disk syndrome; osteopetrosis; thrombosis; silicosis; pulmonary sarcosis; bone resorption diseases, such as osteoporosis or multiple myeloma-related bone disorders; cancer, including but not limited to metastatic breast carcinoma, colorectal carcinoma, malignant melanoma, gastric cancer, or non-small cell lung cancer; graft-versus-host reaction; or autoimmune diseases, such as multiple sclerosis, lupus or fibromyalgia; AIDS or other viral diseases such as Herpes Zoster, Herpes Simplex I or II, influenza virus, Severe Acute Respiratory Syndrome (SARS) or cytomegalovirus; or diabetes mellitus, proliferative disorders (including both benign or malignant hyperplasias), acute myelogenous leukemia, chronic myelogenous leukemia, Kaposi's sarcoma, metastatic melanoma, multiple myeloma, breast cancer, including metastatic breast carcinoma; colorectal carcinoma; malignant melanoma; gastric cancer; non-small cell lung cancer (NSCLC); bone metastases; pain disorders including neuromuscular pain, headache, cancer pain, dental pain, or arthritis pain; angiogenic disorders including solid tumor angiogenesis, ocular neovascularization, or infantile hemangioma; conditions associated with the cyclooxygenase or lipoxygenase signaling pathways, including conditions associated with prostaglandin endoperoxide synthase-2 (including edema, fever, analgesia, or pain); organ hypoxia; thrombin-induced platelet aggregation; or protozoal diseases. For example, IPF and scleroderma (or systemic sclerosis) associated interstitial lung disease (SSc-ILD) share overlapping pathologic pathways, most notably the activation and proliferation of fibroblasts, expression of fibrogenic cytokines and growth factors, and progressive interstitial fibrosis. IPF and SSc-ILD also have biomarkers in common, including CCL 18, SP-A, SP D, KL 6, ICAM-1, VCAM 1, CCL 2, YKL-40, and vWF. In example embodiments, the patient is one who suffers from a fibrotic condition, such as idiopathic pulmonary fibrosis (IPF).

[0012] In some cases, the patient is selected, or diagnosed, or identified to have one or more of the following criteria: (1) ratio of forced expiratory volume in one second (FEV1) to forced vital capacity volume (FVC), or FEV1/FVC, is greater than 0.80, (2) percent of

predicted FVC (%FVC) is 90% or less, for example ranging from 50% to 90%, inclusive of both endpoints, and (3) time since diagnosis of IPF is at least six months and up to 48 months. Alternatively, in these aspects of the invention, the patient is selected, or diagnosed, or identified to have a percent of predicted FVC (%FVC) is 80% or less. Alternatively, in these aspects of the invention, the patient is selected, or diagnosed, or identified to have (1) %FVC that is 90% or less or 80% or less and (2) absence of or borderline obstructive physiology, as determined by a ratio of forced expiratory volume in one second (FEV1) to forced vital capacity volume (FVC) (FEV1/FVC), that is greater than, or equal to, 0.70, or greater than, or equal to, 0.75, or greater than, or equal to, 0.80, or any number between 0.70 and 0.80. Also contemplated is a patient that exhibits (i) percent of predicted forced vital capacity volume (%FVC) of about 80% or less, and optionally that also exhibits (ii) ratio of forced expiratory volume in one second (FEV1) to forced vital capacity volume (FVC) of about 0.70 or greater or 0.80 or greater. In various cases, the patient exhibits (i) percent of predicted forced vital capacity volume (%FVC) of 90% or less or 80% or less and optionally (ii) ratio of forced expiratory volume in one second (FEV1) to forced vital capacity volume (FVC) of about 0.70 or greater or 0.80 or greater. Optionally, in some or any of these embodiments, %FVC ranges from about 50% to 80%. In some or any embodiments, the patient has been diagnosed with pulmonary fibrosis, optionally IPF, for at least six months, and optionally less than 48 months. In some or any embodiments, optionally the patient is also selected to exhibit a percent of diffusing capacity (%DLco) of about 90% or less, for example, ranging from 30% to 90%, or 30% to 60%, inclusive of both endpoints. In some or any embodiments, the FEV1/FVC ratio is greater than 0.75, or in some cases greater than 0.9. In some or any embodiments, the %FVC is less than 75%, 70%, 65%, or 60%. In some or any embodiments, the %DLco is less than 90%, 80%, 70%, 60%, or 50%, or less than 40%. In most cases the patient is diagnosed with IPF through a High Resolution Computed Tomography (HRCT) scan, optionally with confirmation through surgical lung biopsy.

[0013] As used herein, the terms “adverse event” and “adverse reactions” refer to any unfavorable, harmful, or pathologic change in a patient receiving pirfenidone therapy as indicated by physical signs, symptoms, and/or clinically significant laboratory abnormalities that occur in a patient during the treatment and post-treatment period, regardless of suspected cause. Specific AEs that can be reduced by the methods disclosed herein include, but are not limited to nausea, gastric upset, headache, somnolence, photosensitivity, a nervous system disorder, and dizziness. Other specific AEs that can be reduced include upper respiratory tract infection, urinary tract infection, anorexia, decreased appetite, insomnia, dysgeusia, hot

flush, dyspnoea, cough, diarrhea, rash, gastroesophageal reflux disease, vomiting, abdominal distension, abdominal discomfort, abdominal pain, stomach discomfort, gastritis, flatulence, pruritus, erythema, dry skin, rash erythematous, rash macular, rash pruritic, myalgia, arthralgia, asthenia, non-cardiac chest pain, and sunburn.

[0014] In some embodiments, the food is a solid food with sufficient caloric and fat content that it is not rapidly dissolved and absorbed in the stomach. Thus, in some embodiments, the food is a snack or a meal, for example, breakfast, lunch or dinner. In some embodiments, the food is a high fat and/or high calorie meal.

[0015] As used herein, the terms “with food” or “fed conditions” are understood conventionally to mean the condition of administering the drug at about the same time as having consumed food, or shortly after consuming food. The terms “without food,” “fasted,” “fasted conditions,” or “on an empty stomach” are defined to mean the condition of not having consumed food for at least 30 minutes prior to administration of the drug. In some embodiments, food has not been consumed for about 10 hours, about 8 hours, about 6 hours, about 4 hours, or about 2 hours prior to administration of the drug.

[0016] Vismodegib, when administered in combination with pirfenidone, may be taken before or after pirfenidone, or concomitantly.

Dosing and Formulations

Pirfenidone

[0017] In some embodiments, the amount of pirfenidone being administered is at least 800 mg/day, at least 1600 mg/day, at least 1800 mg/day, or at least 2400 or 2403 mg/day.

Pirfenidone can be dosed at a total amount of about 1600 mg to about 3800 mg or about 1600 mg to about 4800 mg per day. The dosage can be divided into two or three doses over the day or given in a single daily dose. In some cases, the pirfenidone is administered in three divided doses.

[0018] Specific amounts of the total daily amount of the therapeutic contemplated for the disclosed methods include about 800 mg, about 900 mg, about 1000 mg, about 1100 mg, about 1200 mg, about 1300 mg, about 1400 mg, about 1450 mg, about 1500 mg, about 1550 mg, about 1600 mg, about 1700 mg, about 1800 mg, about 1900 mg, about 2000 mg, about 2100 mg, about 2200 mg, about 2300 mg, about 2400 mg, about 2450 mg, about 2500 mg, about 2550 mg, about 2600 mg, about 2650 mg, about 2670 mg, about 2700 mg, about 2750 mg, about 2800 mg, about 2850 mg, about 2900 mg, about 2937 mg, about 2950 mg, about 3000 mg, about 3050 mg, about 3100 mg, about 3150 mg, about 3200 mg, about 3204 mg,

about 3250 mg, about 3300 mg, about 3350 mg, about 3400 mg, about 3450 mg, about 3471 mg, about 3500 mg, about 3550 mg, about 3600 mg, about 3650 mg, about 3700 mg, about 3738 mg, about 3750 mg, and about 3800 mg. Any and all ranges utilizing these amounts as endpoints are also contemplated; for example, the daily administered amount can range from about 1600 mg/day to about 4000 mg/day, or from about 1700 mg/day to about 2500 mg/day, or from about 1800 mg/day to about 2500 mg/day, or from about 2300 mg/day to about 2500 mg/day.

[0019] Dosages of pirfenidone can alternately be administered as a dose measured in mg/kg. Contemplated mg/kg doses of the disclosed therapeutics include about 1 mg/kg to about 40 mg/kg. Specific ranges of doses in mg/kg include about 1 mg/kg to about 20 mg/kg, about 5 mg/kg to about 20 mg/kg, about 10 mg/kg to about 20 mg/kg, about 10 mg/kg to about 30 mg/kg, and about 15 mg/kg to about 25 mg/kg. Other specific ranges of doses include about 1 mg/kg to about 35 mg/kg. Specific doses contemplated include about 1 mg/kg, about 2 mg/kg, about 3 mg/kg, about 4 mg/kg, about 5 mg/kg, about 6 mg/kg, about 7 mg/kg, about 8 mg/kg, about 9 mg/kg, about 10 mg/kg, about 11 mg/kg, about 12 mg/kg, about 13 mg/kg, about 14 mg/kg, about 15 mg/kg, about 16 mg/kg, about 17 mg/kg, about 18 mg/kg, about 19 mg/kg, about 20 mg/kg, about 21 mg/kg, about 22 mg/kg, about 23 mg/kg, about 24 mg/kg, about 25 mg/kg, about 26 mg/kg, about 27 mg/kg, about 28 mg/kg, about 29 mg/kg, about 30 mg/kg, about 31 mg/kg, about 32 mg/kg, about 33 mg/kg, about 34 mg/kg, about 35 mg/kg, about 36 mg/kg, about 37 mg/kg, about 38 mg/kg, about 39 mg/kg, about 40 mg/kg.

[0020] The pirfenidone dosing may be once or twice or three times daily, with one or more units per dose. In some embodiments, the effective daily intake of pirfenidone is administered as one, two, three, four, five, six, or more doses administered separately at appropriate intervals throughout the day. In some embodiments, each dose comprises one, two, three or more unit dosage forms. For example, in some embodiments, one or more units are administered to the subject one or more times per day. In some embodiments, one or more units are administered to the subject twice per day. In some embodiments, one or more units are administered to the subject three times per day. In some embodiments, 1 unit is administered three times per day. In some embodiments, 2 units are administered three times per day. In some embodiments, 3 units are administered three times per day. In some embodiments, pirfenidone is administered as multiple doses spaced throughout the day and each dose comprises a therapeutically effective amount of pirfenidone. In some embodiments, pirfenidone is administered with food, e.g. a meal, once per day. In some

embodiments, pirfenidone is administered with food twice per day. In some embodiments, pirfenidone is administered with food thrice (three times) per day. In some embodiments, pirfenidone is administered within about five minutes of the food (before or after) or within 30 minutes after the food, e.g., a meal.

[0021] As used herein, the term “unit dosage form,” refers to physically discrete units suitable as unitary dosages for human and animal subjects, each unit containing a predetermined quantity of pirfenidone calculated in an amount sufficient to produce the desired effect in association with a pharmaceutically acceptable diluent, carrier or vehicle. In some embodiments, the unit dosage form is, for example, a pill, capsule, or tablet. In some embodiments, the unit dosage form is a capsule. In some embodiments, the amount of pirfenidone in a unit dosage form is about 100 mg is up to about 1800 mg, or about 200 mg to about 900 mg, or about 100 mg to about 400 mg. In some embodiments, the unit dosage form comprises about 267 mg of pirfenidone and is in the form of a capsule. In some embodiments, one, two or three capsules, each of which comprises about 267 mg of pirfenidone, are administered to the patient once, twice or three times per day (e.g., a total daily intake of about 534 mg/day to about 2403 mg/day). In some embodiments, the unit dosage form comprises about 200 mg or 267 mg of pirfenidone and is in the form of a tablet. In some embodiments, one, two or three tablets, each of which comprises about 200 mg or 267 mg of pirfenidone, are administered to the patient once, twice, or three times per day (e.g., a total daily intake of about 600 mg/day to about 2403 mg/day).

[0022] In some cases, pirfenidone is formulated in a capsule. The capsule can comprise a pharmaceutical formulation of pirfenidone and includes 5-30% of a pharmaceutically acceptable excipients and 70-95% of pirfenidone by weight.

[0023] The excipients of the pirfenidone formulation, in some cases a capsule, include disintegrators, binders, fillers, and lubricants. Examples of disintegrators include agar-agar, algin, calcium carbonate, carboxymethylcellulose, cellulose, clays, colloid silicon dioxide, croscarmellose sodium, crospovidone, gums, magnesium aluminium silicate, methylcellulose, polacrillin potassium, sodium alginate, low substituted hydroxypropylcellulose, and cross-linked polyvinylpyrrolidone hydroxypropylcellulose, sodium starch glycolate, and starch. Examples of binders include microcrystalline cellulose, hydroxymethyl cellulose, hydroxypropylcellulose, and polyvinylpyrrolidone. Examples of fillers include calcium carbonate, calcium phosphate, dibasic calcium phosphate, tribasic calcium sulfate, calcium carboxymethylcellulose, cellulose, dextrin derivatives, dextrin, dextrose, fructose, lactitol,

lactose, magnesium carbonate, magnesium oxide, maltitol, maltodextrins, maltose, sorbitol, starch, sucrose, sugar, and xylitol. Examples of lubricants include agar, calcium stearate, ethyl oleate, ethyl laureate, glycerin, glyceryl palmitostearate, hydrogenated vegetable oil, magnesium oxide, magnesium stearate, mannitol, poloxamer, glycols, sodium benzoate, sodium lauryl sulfate, sodium stearyl, sorbitol, stearic acid, talc, and zinc stearate.

[0024] In some cases, a pirfenidone formulation is disclosed that is by weight 2-10% disintegrator, 2-30% binder, 2-30% filler, and 0.3-0.8% lubricant. In some cases, by weight 2-10% of the capsule is disintegrator, 2-25% is binder, 2-25% is filler, and 0.3-0.8% is lubricant. In some cases, the excipients further include povidone. In various cases, by weight 1-4% of the capsule is povidone. According to various cases, the capsule includes 100-400 mg pirfenidone.

[0025] Disintegrators, as used herein, refer to one or more of agar-agar, algin, calcium carbonate, carboxymethylcellulose, cellulose, clays, colloid silicon dioxide, croscarmellose sodium, crospovidone, gums, magnesium aluminium silicate, methylcellulose, polacrillin potassium, sodium alginate, low substituted hydroxypropylcellulose, and cross-linked polyvinylpyrrolidone hydroxypropylcellulose, sodium starch glycolate, and starch.

[0026] Binders, as used herein, refer to one or more of microcrystalline cellulose, hydroxymethyl cellulose, hydroxypropylcellulose, and polyvinylpyrrolidone.

[0027] Fillers, as used herein, refer to one or more of calcium carbonate, calcium phosphate, dibasic calcium phosphate, tribasic calcium sulfate, calcium carboxymethylcellulose, cellulose, dextrin derivatives, dextrin, dextrose, fructose, lactitol, lactose, magnesium carbonate, magnesium oxide, maltitol, maltodextrins, maltose, sorbitol, starch, sucrose, sugar, and xylitol.

[0028] Lubricants, as used herein, refer to one or more of agar, calcium stearate, ethyl oleate, ethyl laureate, glycerin, glyceryl palmitostearate, hydrogenated vegetable oil, magnesium oxide, magnesium stearate, mannitol, poloxamer, glycols, sodium benzoate, sodium lauryl sulfate, sodium stearyl, sorbitol, stearic acid, talc, and zinc stearate.

[0029] Capsule, as used herein, refers to a generally safe, readily dissolvable enclosure for carrying certain pharmaceutical products. In some cases, capsule is made of gelatin. Other suitable matrix substances such as total synthetic polymer chemicals having gelatin-like properties may be used to manufacture pirfenidone capsules.

[0030] In various embodiments, the pirfenidone formulation can be an intrapulmonary dosage form, for example, a solution or powder suitable for aerosolization or nebulization, or an inhalable powder.

Vismodegib

[0031] The amount of vismodegib being administered is at least 100 mg, at least 150 mg, or at least 200 mg/day. For example, vismodegib can be dosed at a total amount of about 100 mg to about 2000 mg per day. The dosage can be divided into two or three doses over the day or given in a single daily dose. Specific amounts of the total daily amount of the therapeutic contemplated for the disclosed methods include about 100 mg, about 145 mg, about 150 mg, about 155 mg, about 200 mg, about 250 mg, about 300 mg, about 350 mg, about 400 mg, about 450 mg, and about 500 mg. Any and all ranges utilizing these amounts of vismodegib as endpoints are also contemplated; for example, about 100 mg to about 150 mg per day, or about 145 mg to about 155 mg per day, or about 200 mg to about 300 mg per day, or from about 100 mg to about 500 mg per day. In some embodiments, the amount of vismodegib being administered is about 150 mg.

[0032] Dosages of vismodegib can alternately be administered as a dose measured in mg/kg. Contemplated mg/kg doses of the disclosed therapeutics include about 1 mg/kg to about 40 mg/kg. Specific ranges of doses in mg/kg include about 1 mg/kg to about 20 mg/kg, about 5 mg/kg to about 20 mg/kg, about 10 mg/kg to about 20 mg/kg, about 10 mg/kg to about 30 mg/kg, and about 15 mg/kg to about 25 mg/kg. Other specific ranges of doses include about 1 mg/kg to about 35 mg/kg. Specific doses contemplated include about 1 mg/kg, about 2 mg/kg, about 3 mg/kg, about 4 mg/kg, about 5 mg/kg, about 6 mg/kg, about 7 mg/kg, about 8 mg/kg, about 9 mg/kg, about 10 mg/kg, about 11 mg/kg, about 12 mg/kg, about 13 mg/kg, about 14 mg/kg, about 15 mg/kg, about 16 mg/kg, about 17 mg/kg, about 18 mg/kg, about 19 mg/kg, about 20 mg/kg, about 21 mg/kg, about 22 mg/kg, about 23 mg/kg, about 24 mg/kg, about 25 mg/kg, about 26 mg/kg, about 27 mg/kg, about 28 mg/kg, about 29 mg/kg, about 30 mg/kg, about 31 mg/kg, about 32 mg/kg, about 33 mg/kg, about 34 mg/kg, about 35 mg/kg, about 36 mg/kg, about 37 mg/kg, about 38 mg/kg, about 39 mg/kg, about 40 mg/kg.

[0033] In various embodiments, the vismodegib formulation can be an oral dosage form selected from the group consisting of a hard gelatin capsule, a soft gelatin capsule, a caplet, or combinations thereof.

Pirfenidone and vismodegib together

[0034] In the methods and uses described herein, pirfenidone is administered together with vismodegib. Any of the ranges described herein for either drug may be combined together. For example, about 100-200 mg/day vismodegib is administered with about 1600-4000 mg/day pirfenidone. As another example, about 100 mg/day to about 150 mg/day of vismodegib is administered with about 2300 mg/day to about 2500 mg/day pirfenidone. As another example, about 145 mg/day to about 155 mg/day of vismodegib is administered with about 2300 mg/day to about 2500 mg/day pirfenidone. More specifically, about 150 mg/day of vismodegib can be administered with about 2400/day or 2403 mg/day of pirfenidone.

[0035] When administered together, the vismodegib can be administered before or after pirfenidone, for example, about 30 minutes before pirfenidone, and the pirfenidone may be administered with food. In example embodiments, the vismodegib is administered with food, or under fasted conditions. For example, vismodegib is administered about 30 minutes prior to eating food, e.g., a meal, and pirfenidone is administered with food, for example, a meal. In some embodiments, vismodegib and pirfenidone are administered concomitantly.

EXAMPLES

[0036] This example is a study of oral vismodegib in patients with mild to moderate Idiopathic Pulmonary Fibrosis (IPF), with administration of pirfenidone, under fed conditions, three times per day at a total daily dose of 2403 mg. The pirfenidone is administered with or shortly after a meal. Vismodegib (150 mg) is administered orally once daily. Vismodegib is administered at least 30 minutes before administration of pirfenidone.

[0037] Approximately 20 patients are treated in a single arm study. Enrolled patients will have already received treatment with pirfenidone at a dose of 1602-2403 milligram (mg)/day for a minimum of 24 weeks prior to screening. If enrolled patients have not already received treatment with pirfenidone, then those patients will received stable treatment with pirfenidone at a dose of 2403 mg/day for the 4 weeks prior to and during screening.

[0038] If patients miss a scheduled dose of study treatment, that dose should be skipped. Regular dosing should resume with the next scheduled dose. Patients should not take any extra doses to make up for missed doses.

[0039] For pirfenidone: Dose adjustments, down titration and dose interruptions of the background treatment shall be prescribed according to the Esbriet® (pirfenidone) SmPC. To summarize, Gastrointestinal events: In patients who experience intolerance to therapy due to

gastrointestinal side effects, patients should be reminded to take the medicinal product with food. If symptoms persist, pirfenidone may be reduced to 1-2 capsules (267 mg – 534 mg) 2-3 times/day with food with re-escalation to the recommended daily dose as tolerated. If symptoms continue, patients may be instructed to interrupt treatment for 1 to 2 weeks to allow symptoms to resolve. Photosensitivity reaction or rash: Patients who experience a mild to moderate photosensitivity reaction or rash should be reminded of the instruction to use a sunblock daily and to avoid sun exposure. The dose of pirfenidone may be reduced to 3 capsules/day (1 capsule three times a day). If the rash persists after 7 days, pirfenidone should be discontinued for 15 days, with re-escalation to the recommended daily dose in the same manner as the dose escalation period. Patients who experience severe photosensitivity reaction or rash should be instructed to interrupt the dose and to seek medical advice. Once the rash has resolved, pirfenidone may be re-introduced and re-escalated up to the recommended daily dose at the discretion of the physician. Hepatic function: In the event of significant elevation of alanine and /or aspartate aminotransferases (ALT/AST) with or without bilirubin elevation, the dose of pirfenidone should be adjusted or treatment discontinued according to the guidelines listed in section 4.4 of the Esbriet SmPC.

[0040] Eligible patients have a confident diagnosis of IPF based on clinical, radiological, and pathological data without evidence or suspicion of an alternative diagnosis that may contribute to their interstitial lung disease. Patients fulfill all of the following inclusion criteria to be eligible for enrolment in the study:

[0041] Diagnosis of IPF: Diagnosis of IPF ≥ 3 months and ≤ 6 years; Age 40-80 years inclusive; Diagnosis of IPF by usual interstitial pneumonia (UIP) pattern in high-resolution computed tomography (HRCT) scan and surgical lung biopsy (SLB), if necessary and available. A previous HRCT will be used and assessed by a central Reading Committee; Extent of fibrotic changes (honeycombing, reticular changes) greater than the extent of emphysema on the HRCT scan; No features supporting an alternative diagnosis on SLB, transbronchial biopsy (TBB), or bronchoalveolar lavage (BAL), if available.

[0042] IPF Disease Severity and Progression: Percent predicted forced vital capacity (FVC) $\geq 50\%$ and $\leq 100\%$ at Screening; Percent predicted carbon monoxide diffusing capacity (DLCO) $\geq 30\%$ and $\leq 90\%$ at Screening; Relative change in pre- and post-bronchodilator FVC (measured in litres) between Screening and Day 1 must be $< 10\%$, calculated as follows: $(\text{Screen FVC (L)} - \text{Day 1 FVC (L)}) / (\text{Screen FVC (L)}) \times 100\%$; Forced expiratory volume in 1 second (FEV1)/FVC ratio ≥ 0.75 at Screening.

[0043] Exclusions from Patients with any of the following exclusion criteria will be excluded from the study: known hypersensitivity to any of the study drug excipients or the drugs themselves; prior treatment with vismodegib or any Hh-pathway inhibitor; evidence of other known causes of interstitial lung disease; hospitalization due to an exacerbation of IPF within 4 weeks prior to or during screening; lung transplant expected within 6 months of screening; evidence of clinically significant lung disease other than IPF; post-bronchodilator forced expiratory volume in 1 second/FVC ratio <0.7 at screening; any clinically significant medical disease (other than IPF) that is associated with an expected survival of <6 months, likely to require a change in therapy during the study; Class IV New York Heart Association chronic heart failure or historical evidence of left ventricular ejection fraction $<35\%$; known current malignancy or current evaluation for a potential malignancy; known immunodeficiency, including, but not limited to, human immunodeficiency virus infection, clinically significant abnormality on electrocardiogram or laboratory tests (hematology, serum chemistry, and urinalysis) at screening, known or suspected peptic ulcer, known achalasia, esophageal stricture, or esophageal dysfunction sufficient to limit the ability to swallow oral medication; tobacco smoking within 3 months of screening or unwillingness to avoid smoking throughout the study; history of alcohol, drug, or chemical abuse that would, in the opinion of the investigator, impair or risk the participant's full participation in the study; abnormal liver function tests results; creatinine clearance <30 milliliter per minute, calculated using the Cockcroft-Gault formula; pregnant or lactating; chronic treatment with any of the following within 4 weeks or five half-lives (whichever is longer) prior to enrollment visit (Day 1/Visit 2): immunosuppressive or immunomodulatory therapies, chronic oral corticosteroid therapy, pulmonary hypertension therapies, oral itraconazole, tyrosine kinase inhibitors, strong inhibitors of cytochrome P450 (CYP)1A2, moderate inducers of CYP1A2, and cytotoxic drugs, warfarin or other anticoagulant therapy, and any unlicensed therapy if used for IPF indication; any condition that, as assessed by the investigator, might be significantly exacerbated by the known side effects associated with pirfenidone.

[0044] The dose of study medication can be adjusted or suspended if an AE occurs, according to the investigator and the dose modification guidelines within the protocol.

What is Claimed:

1. A method comprising administering to a patient (i) vismodegib in a total daily amount of about 100 mg/day to about 200 mg/day; and (ii) pirfenidone optionally with food, in a total daily amount of at least 1600 mg/day to about 3000 mg/day.
2. The method of claim 1, wherein the vismodegib is administered at least 30 minutes prior to administering the pirfenidone.
3. The method of any one of claims 1 to 2, wherein the pirfenidone is administered at about 1800 mg/day.
4. The method of any one of claims 1 to 2, wherein the pirfenidone is administered at about 2300 mg/day to about 2500 mg/day.
5. The method of any one of claims 1, 2 or 4, wherein the pirfenidone is administered at 2400 mg/day or 2403 mg/day.
6. The method of any one of claims 1 to 5, wherein the vismodegib is administered at about 145 mg/day to about 155 mg/day.
7. The method of any one of claims 1 to 6, wherein the vismodegib is administered at about 150 mg/day.
8. The method of any one of claims 1 to 7, wherein the pirfenidone is administered in two or three divided doses.
9. The method of any one of claims 1 to 8, wherein the pirfenidone is formulated in a capsule.
10. The method of any one of claims 1 to 8, wherein the pirfenidone is formulated in a tablet.
11. The method of any one of claims 1 to 10, wherein the vismodegib is administered in one dose.
12. The method of any one of claims 1 to 11, wherein the vismodegib is formulated in a capsule.
13. The method of any one of claims 1 to 12, wherein the food is a meal.
14. The method of any one of claims 1 to 13, wherein the vismodegib is administered at least 30 minutes before food.

15. The method of claim 13 or 14, wherein the pirfenidone is administered at the same time as or within 30 minutes after a meal.
16. The method of any one of claims 1 to 15, wherein the vismodegib is administered under fasted conditions.
17. The method of any one of claims 1 to 15, wherein the vismodegib is administered with food.
18. The method of any one of claims 1 to 17, wherein the patient suffers from idiopathic pulmonary fibrosis, pulmonary fibrosis, bronchiolitis obliterans, chronic lung transplant rejection, scleroderma, primary focal segmental glomerulosclerosis (FSGC) or membranoproliferative glomerulonephritis (MPGN), idiopathic interstitial pneumonia, interstitial lung disease in systemic sclerosis, a fibrosis condition of the lung, autoimmune lung diseases, benign prostate hypertrophy, coronary or myocardial infarction, atrial fibrillation, cerebral infarction, myocardial fibrosis, musculoskeletal fibrosis, post-surgical adhesions, liver cirrhosis, renal fibrotic disease, fibrotic vascular disease, scleroderma, Hermansky-Pudlak syndrome, neurofibromatosis, Alzheimer's disease, diabetic retinopathy, or skin lesions, lymph node fibrosis associated with HIV, chronic obstructive pulmonary disease (COPD), inflammatory pulmonary fibrosis, rheumatoid arthritis; rheumatoid spondylitis; osteoarthritis; gout, other arthritic conditions; sepsis; septic shock; endotoxic shock; gram-negative sepsis; toxic shock syndrome; myofascial pain syndrome (MPS); Shigellosis; asthma; adult respiratory distress syndrome; inflammatory bowel disease; Crohn's disease; psoriasis; eczema; ulcerative colitis; glomerular nephritis; scleroderma; chronic thyroiditis; Grave's disease; Ormond's disease; autoimmune gastritis; myasthenia gravis; autoimmune hemolytic anemia; autoimmune neutropenia; thrombocytopenia; pancreatic fibrosis; chronic active hepatitis including hepatic fibrosis; acute or chronic renal disease; renal fibrosis; diabetic nephropathy; irritable bowel syndrome; pyresis; restenosis; cerebral malaria; stroke or ischemic injury; neural trauma; Alzheimer's disease; Huntington's disease; Parkinson's disease; acute or chronic pain; allergies, including allergic rhinitis or allergic conjunctivitis; cardiac hypertrophy, chronic heart failure; acute coronary syndrome; cachexia; malaria; leprosy; leishmaniasis; Lyme disease; Reiter's syndrome; acute synovitis; muscle degeneration, bursitis; tendonitis; tenosynovitis; herniated, ruptured, or prolapsed intervertebral disk syndrome; osteopetrosis; thrombosis; silicosis; pulmonary sarcosis; bone resorption diseases, such as osteoporosis or multiple myeloma-related bone disorders; cancer, including but not limited to metastatic breast carcinoma, colorectal carcinoma, malignant

melanoma, gastric cancer, or non-small cell lung cancer; graft-versus-host reaction; or autoimmune diseases, such as multiple sclerosis, lupus or fibromyalgia; AIDS or other viral diseases such as Herpes Zoster, Herpes Simplex I or II, influenza virus, Severe Acute Respiratory Syndrome (SARS) or cytomegalovirus; or diabetes mellitus, proliferative disorders (including both benign or malignant hyperplasias), acute myelogenous leukemia, chronic myelogenous leukemia, Kaposi's sarcoma, metastatic melanoma, multiple myeloma, breast cancer, including metastatic breast carcinoma; colorectal carcinoma; malignant melanoma; gastric cancer; non-small cell lung cancer (NSCLC); bone metastases; pain disorders including neuromuscular pain, headache, cancer pain, dental pain, or arthritis pain; angiogenic disorders including solid tumor angiogenesis, ocular neovascularization, or infantile hemangioma; conditions associated with the cyclooxygenase or lipoxygenase signaling pathways, including conditions associated with prostaglandin endoperoxide synthase-2 (including edema, fever, analgesia, or pain); organ hypoxia; thrombin-induced platelet aggregation; or protozoal diseases.

19. The method of any one of claims 1 to 18, wherein the patient suffers from a fibrotic condition.

20. The method of any one of claims 1 to 19, wherein the patient suffers from idiopathic pulmonary fibrosis.

21. The method of any one of claims 1 to 20, further comprising administering pirfenidone, in a total daily amount at least 1600 mg/day to about 3000 mg/day for four weeks prior to administering vismodegib and pirfenidone.

22. The method of any one of claims 1 to 21, wherein the patient was treated with pirfenidone, in a total daily amount at least 1600 mg/day to about 3000 mg/day for at least twenty-four weeks prior to the administration of vismodegib.

23. The method of any one of claims 21 to 22, wherein the total daily amount of pirfenidone is 2403 mg/day.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2016/080354

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/4418 A61P11/00
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 A61P

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, FSTA, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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Further documents are listed in the continuation of Box C.



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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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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Date of the actual completion of the international search

27 February 2017

Date of mailing of the international search report

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Name and mailing address of the ISA/

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INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2016/080354

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International application No

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