SPARSENTAN FOR TREATING IDIOPATHIC PULMONARY FIBROSIS

FIELD

[0001] Provided herein are methods of treating idiopathic pulmonary fibrosis (IPF), comprising administering a therapeutically effective amount of a dual-acting angiotensin and endothelin receptor antagonist (DARA). Provided herein are also pharmaceutical formulations that are suitable for such administration.

BACKGROUND

[0002] Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive, fibrotic interstitial lung disease of unknown cause. IPF affects the lung interstitium, the tissue residing between the alveoli which is dense with capillaries in order to facilitate gas exchange during respiration. Recurrent, subclinical epithelial injury superimposed on accelerated epithelial aging leads to aberrant repair of the injured alveolus and deposition of interstitial fibrosis by myofibroblasts. Fibrosis of the lung interstitium leads to inefficient gas exchange, causing progressive and irreversible decline in lung function, leading to cough, dyspnea, low forced vital lung capacity, and impaired quality of life. While certain risk factors have been identified, including environmental exposures, smoking, gastroesophageal reflux disease, certain infections, and genetic predisposition, the specific route of pathogenesis for idiopathic pulmonary fibrosis is currently unknown.

[0003] The clinical course of IPF varies widely between patients, with some patients' disease progress defined by a relatively slow decline in lung function, while other patients' symptoms rapidly worsen. Patients with IPF may experience periods of relative stability interspersed with periods of acute worsening. Patients' disease progression can be monitored using various test. Forced vital capacity (FVC) is the total amount of air a person can exhale rapidly and with maximum force after taking the deepest breath possible. FVC is measured in liters using a spirometry lung function. FVC results are often reported as "percent predicted FVC," and is scaled relative to gender, age, and height considerations, with a lower score indicating worse lung function. Changes in percent predicted FVC are a useful metric in measuring IPF progression. A decrease in FVC scores of 10% is considered a "meaningful" drop, and is indicative of disease progression. A drop of less than 10% usually indicates disease stability. Similarly, measurement of the diffusing capacity of carbon monoxide (DLCO) is a useful test for pulmonary function, and can be used to estimate the transfer of oxygen from the alveoli in the lungs to the red blood cells in the bloodstream. As with FVC testing, DLCO tests are reported as "percent predicted DLCO," and are scaled relative to ethnicity, gender, age, and height, with a lower score indicating worse oxygen transfer in the lungs. A DLCO result of 80% of the predicted value or higher is within the normal range. A drop in the percent predicted DLCO score of 15% or more between examinations indicates worsening lung damage. Also, high-resolution computed tomography

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(HRCT) imaging can be used to visualize distinctive lung patterns present in IPF patients, indicative of scar tissue formation.

[0004] According to the National Institutes of Health, idiopathic pulmonary fibrosis affects approximately 13 to 20 individuals per 100,000 worldwide (approximately 3 million people), with an estimated 100,000 people affected in the United States alone. Each year, 30,000 to 40,000 new cases are diagnosed in the United States. For those stricken with IPF, only approximately 20-30% survive beyond 5 years after diagnosis.

[0005] Current management for IPF includes treatment with nintedanib, a tyrosine kinase inhibitor, or pirfenidone, an inhibitor of TGF-β production, collagen synthesis, and fibroblast proliferation. While these treatments slow IPF progression, they do not stop or reverse the damage caused by the disease. Side effects of these treatments include diarrhea, gastrointestinal distress, nausea, disinterest in eating, and photosensitivity, which limit patient tolerability of treatment, and cause approximately 30% of patients to discontinue treatment within 2 years.

[0006] A need exists for therapeutic agents for treating idiopathic pulmonary fibrosis.

SUMMARY

[0007] Provided herein are methods for treating idiopathic pulmonary fibrosis, comprising administering a therapeutically effective amount of a dual-acting angiotensin and endothelin receptor antagonist to a patient in need thereof.

[0008] Provided herein are methods for treating idiopathic pulmonary fibrosis, comprising administering a therapeutically effective amount of sparsentan, or a pharmaceutically acceptable salt thereof, to a patient in need thereof.

[0009] Also provided herein are methods for treating idiopathic pulmonary fibrosis, comprising administering a composition, comprising a therapeutically effective amount of a sparsentan, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, to a patient in need thereof.

[0010] Also provided herein are methods of suppressing lung epithelial inflammation and fibrosis in a patient in need thereof, comprising administering to the patient an effective amount of a dual-acting angiotensin and endothelin receptor antagonist.

CONFIDENTIAL

[0011] Also provided herein are methods of suppressing lung myofibroblast phenotypic transition in a patient in need thereof, comprising administering to the patient an effective amount of a dual-acting angiotensin and endothelin receptor antagonist.

[0012] Also provided herein are methods for treating idiopathic pulmonary fibrosis, comprising administering an effective amount of a dual-acting angiotensin and endothelin receptor antagonist to a patient in need thereof, wherein said patient has a genetic mutation in the MUC5B, TERT, TERC, RTEL1, PARN, SFTPC, or SFTPA2 genes.

[0013] Also provided herein are methods for treating idiopathic pulmonary fibrosis, comprising administering an effective amount of a dual-acting angiotensin and endothelin receptor antagonist to a patient in need thereof, wherein said patient is 50 years of age or older.

[0014] Also provided herein are methods for treating idiopathic pulmonary fibrosis, comprising administering an effective amount of a dual-acting angiotensin and endothelin receptor antagonist to a patient in need thereof, wherein said patient is a smoker.

[0015] Also provided herein are methods for treating idiopathic pulmonary fibrosis, comprising administering an effective amount of a dual-acting angiotensin and endothelin receptor antagonist to a patient in need thereof, wherein said patient also suffers from gastroesophageal reflux disease.

[0016] Also provided herein are methods for treating idiopathic pulmonary fibrosis, comprising administering a therapeutically effective amount of sparsentan, or a pharmaceutically acceptable salt thereof, to a patient in need thereof.

[0017] Also provided herein are methods for treating idiopathic pulmonary fibrosis, comprising administering a composition, comprising a therapeutically effective amount of sparsentan and a pharmaceutically acceptable carrier, to a patient in need thereof.

[0018] Also provided herein are methods of suppressing lung epithelial inflammation and fibrosis in a patient in need thereof, comprising administering to the patient an effective amount of sparsentan, or a pharmaceutically acceptable salt thereof.

[0019] Also provided herein are methods of suppressing lung myofibroblast phenotypic transition in a patient in need thereof, comprising administering to the patient an effective amount of sparsentan, or a pharmaceutically acceptable salt thereof.

[0020] Also provided herein are methods for treating idiopathic pulmonary fibrosis, comprising administering an effective amount of sparsentan, or a pharmaceutically acceptable salt thereof, to a patient in

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need thereof, wherein said patient has a genetic mutation in the MUC5B, TERT, TERC, RTEL1, PARN, SFTPC, or SFTPA2 genes.

[0021] Also provided herein are methods for treating idiopathic pulmonary fibrosis, comprising administering an effective amount of sparsentan, or a pharmaceutically acceptable salt thereof, to a patient in need thereof, wherein said patient is 50 years of age or older.

[0022] Also provided herein are methods for treating idiopathic pulmonary fibrosis, comprising administering an effective amount of sparsentan, or a pharmaceutically acceptable salt thereof, to a patient in need thereof, wherein said patient is a smoker.

[0023] Also provided herein are methods for treating idiopathic pulmonary fibrosis, comprising administering an effective amount of sparsentan, or a pharmaceutically acceptable salt thereof, to a patient in need thereof, wherein said patient also suffers from gastroesophageal reflux disease.

BRIEF DESCRIPTION OF THE FIGURES

[0024] FIG. 1 shows body weight change for mouse test groups over the course of study, with an untreated group, a group treated only with oral gavage vehicle comprising 10% DMSO, 40% PEG300, 5% Tween-80, and 45% saline, a reference group which received nintedanib, and a group treated with sparsentan. The group treated with sparsentan lost less weight and regained more weight as compared to the reference group treated with nintedanib.

[0025] FIG. 2 shows Masson Trichrome scores for lung tissue collagen staining of samples collected from an untreated group, a group treated only with oral gavage vehicle comprising 10% DMSO, 40% PEG300, 5% Tween-80, and 45% saline, a reference group which received nintedanib, and a group treated with sparsentan. The group treated with sparsentan displayed a slight decrease in collagen staining in lung tissue as compared with the reference group treated with nintedanib.

[0026] FIG. 3 shows average histopathology scores for lung infiltration of neutrophils for samples collected from an untreated group, a group treated only with oral gavage vehicle comprising 10% DMSO, 40% PEG300, 5% Tween-80, and 45% saline, a reference group which received nintedanib, and a group treated with sparsentan. The group treated with sparsentan displayed a marked decrease in lung neutrophils observed as compared to the reference group treated with nintedanib.

[0027] FIG. 4 shows average histopathology scores for lung infiltration of lymphocytes for samples collected from an untreated group, a group treated only with oral gavage vehicle comprising 10% DMSO, 40% PEG300, 5% Tween-80, and 45% saline, a reference group which received nintedanib, and a group treated with sparsentan. The group treated with sparsentan displayed a decrease in lymphocytes when compared to the reference group treated with nintedanib.

CONFIDENTIAL

[0028] FIG. 5 shows concentration of TGF-β in bronchoalveolar lavage fluid (BALF) samples collected on day 21 from an untreated group, a group treated only with oral gavage vehicle comprising 10% DMSO, 40% PEG300, 5% Tween-80, and 45% saline, a reference group which received nintedanib, and a group treated with sparsentan.

[0029] FIG. 6 shows the concentration of $CD45^+$ cells in bronchoalveolar lavage fluid (BALF) samples collected on day 21 (after lung collection), from an untreated group, a group treated only with oral gavage vehicle comprising 10% DMSO, 40% PEG300, 5% Tween-80, and 45% saline, a reference group which received nintedanib, and a group treated with sparsentan.

[0030] FIG. 7 shows the frequency of macrophages ($CD45^+$, Siglec F^+, $CD11c^+$) observed in bronchoalveolar lavage fluid (BALF) samples collected on day 21 (after lung collection), from an untreated group, a group treated only with oral gavage vehicle comprising 10% DMSO, 40% PEG300, 5% Tween-80, and 45% saline, a reference group which received nintedanib, and a group treated with sparsentan.

[0031] FIG. 8 shows the frequency of B-cells ($CD45^+$, Siglec F^-, $CD11c^-$, $B220^+$) observed in bronchoalveolar lavage fluid (BALF) samples collected on day 21 (after lung collection), from an untreated group, a group treated only with oral gavage vehicle comprising 10% DMSO, 40% PEG300, 5% Tween-80, and 45% saline, a reference group which received nintedanib, and a group treated with sparsentan.

[0032] FIG. 9 shows the frequency of T-cells ($CD45^+$, Siglec F^-, $CD11c^-$, $CD3^+$) observed in bronchoalveolar lavage fluid (BALF) samples collected on day 21 (after lung collection), from an untreated group, a group treated only with oral gavage vehicle comprising 10% DMSO, 40% PEG300, 5% Tween-80, and 45% saline, a reference group which received nintedanib, and a group treated with sparsentan.

[0033] FIG. 10 shows the frequency of neutrophils ($CD45^+$, Siglec F^-, $CD11c^-$, Ly-$6G^+$) observed in bronchoalveolar lavage fluid (BALF) samples collected on day 21 (after lung collection), from an untreated group, a group treated only with oral gavage vehicle comprising 10% DMSO, 40% PEG300, 5% Tween-80, and 45% saline, a reference group which received nintedanib, and a group treated with sparsentan.

DETAILED DESCRIPTION

Definitions

[0034] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of ordinary skill in the art. As used herein, the below terms have the following meanings unless specified otherwise. Any methods, devices and materials similar or equivalent to those described herein can be used in the practice of the compositions and methods described herein. The following definitions are provided to facilitate understanding of certain terms used frequently herein and are

CONFIDENTIAL

not meant to limit the scope of the present disclosure. All references referred to herein are incorporated by reference in their entirety.

[0035] It is noted here that as used in this specification and the appended claims, the singular forms "a" "an" and "the" and the like include plural referents unless the context clearly dictates otherwise.

[0036] The term "about" or "approximately" means within ± 30%, 20%, 15%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1%, 0.5%, or 0.05% of a given value or range. In some embodiments, "about" means ± 5% of a given value or range. In some embodiments, "about" means ± 4% of a given value or range. In some embodiments, "about" means ± 3% of a given value or range. In some embodiments, "about" means ± 2% of a given value or range. In some embodiments, "about" means ± 1% of a given value or range. In another embodiment, about means ± 0.5% of a given value or range. In some embodiments, "about" means ± 0.05% of a given value or range.

[0037] "Pharmaceutically acceptable" or "physiologically acceptable" refer to compounds, salts, compositions, dosage forms and other materials which are useful in preparing a pharmaceutical composition that is suitable for human or veterinary pharmaceutical use.

[0038] The term "pharmaceutically acceptable salt" of a given compound refers to salts that retain the biological effectiveness and properties of the given compound, and which are not biologically or otherwise undesirable. "Pharmaceutically acceptable salts" or "physiologically acceptable salts" include, for example, salts with inorganic acids and salts with an organic acid. In addition, if the compounds described herein are obtained as an acid addition salt, the free base can be obtained by basifying a solution of the acid salt. Conversely, if the product is a free base, an addition salt, particularly a pharmaceutically acceptable addition salt, may be produced by dissolving the free base in a suitable organic solvent and treating the solution with an acid, in accordance with conventional procedures for preparing acid addition salts from base compounds. Those skilled in the art will recognize various synthetic methodologies that may be used to prepare nontoxic pharmaceutically acceptable addition salts. Pharmaceutically acceptable acid addition salts may be prepared from inorganic and organic acids. Salts derived from inorganic acids include hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like. Salts derived from organic acids include acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, malic acid, malonic acid, succinic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluene-sulfonic acid, salicylic acid, and the like. Likewise, pharmaceutically acceptable base addition salts can be prepared from inorganic and organic bases. Salts derived from inorganic bases include, by way of example only, sodium, potassium, lithium, ammonium, calcium and magnesium salts. Salts derived from organic bases include, but are not limited to, salts of primary, secondary and tertiary

CONFIDENTIAL

amines. Specific examples of suitable amines include, by way of example only, isopropylamine, trimethyl amine, diethyl amine, tri(iso-propyl) amine, tri(n-propyl) amine, ethanolamine, 2-dimethylaminoethanol, piperazine, piperidine, morpholine, N-ethylpiperidine, and the like.

[0039] As used herein, the term "administration" refers to introducing an agent into a patient. For example, a therapeutic amount can be administered to the patient, which can be determined by the treating physician, medical professional, or the like. In some embodiments, an oral route of administration is preferred. The related terms and phrases "administering" and "administration of," when used in connection with a compound or tablet (and grammatical equivalents) refer both to direct administration, which may be administration to a patient by a medical professional or by self-administration by the patient, and/or to indirect administration, which may be the act of prescribing a drug. Administration entails delivery to the patient of the drug.

[0040] The term "dose" or "dosage" refers to the total amount of an active agent (e.g., sparsentan or a pharmaceutically acceptable salt thereof) administered to a patient in a single day (24-hour period). The desired dose can be administered once daily. In some embodiments, the desired dose may be administered in one, two, three, four or more sub-doses at appropriate intervals throughout the day, where the cumulative amount of the sub-doses equals the amount of the desired dose administered in a single day. The terms "dose" and "dosage" are used interchangeably herein.

[0041] As used herein, "therapeutically effective amount" or "therapeutic amount" refers to an amount of a drug or an agent (e.g., sparsentan or a pharmaceutically acceptable salt thereof) that when administered to a patient suffering from a condition, will have the intended therapeutic effect, e.g., alleviation, amelioration, palliation or elimination of one or more manifestations of the condition in the patient. The full therapeutic effect does not necessarily occur by administration of one dose, and can occur only after administration of a series of doses and can be administered in one dose form or multiples thereof. Thus, a therapeutically effective amount may be administered in one or more administrations.

[0042] As used herein, the term "patient" refers to a mammal, such as a human, bovine, rat, mouse, dog, monkey, ape, goat, sheep, cow, or deer. A patient as described herein can be a human.

[0043] As used herein, "treatment," "treating," and "treat" are defined as acting upon a disease, disorder, or condition with an agent to reduce or ameliorate the harmful or any other undesired effects of the disease, disorder, or condition and/or its symptoms. Treatment, as used herein, covers the treatment of a human patient, and includes: (a) reducing the risk of occurrence of the condition in a patient determined to be predisposed to the disease but not yet diagnosed as having the condition, (b) impeding the development of the

CONFIDENTIAL

condition, and/or (c) relieving the condition, i.e., causing regression of the condition and/or relieving one or more symptoms of the condition.

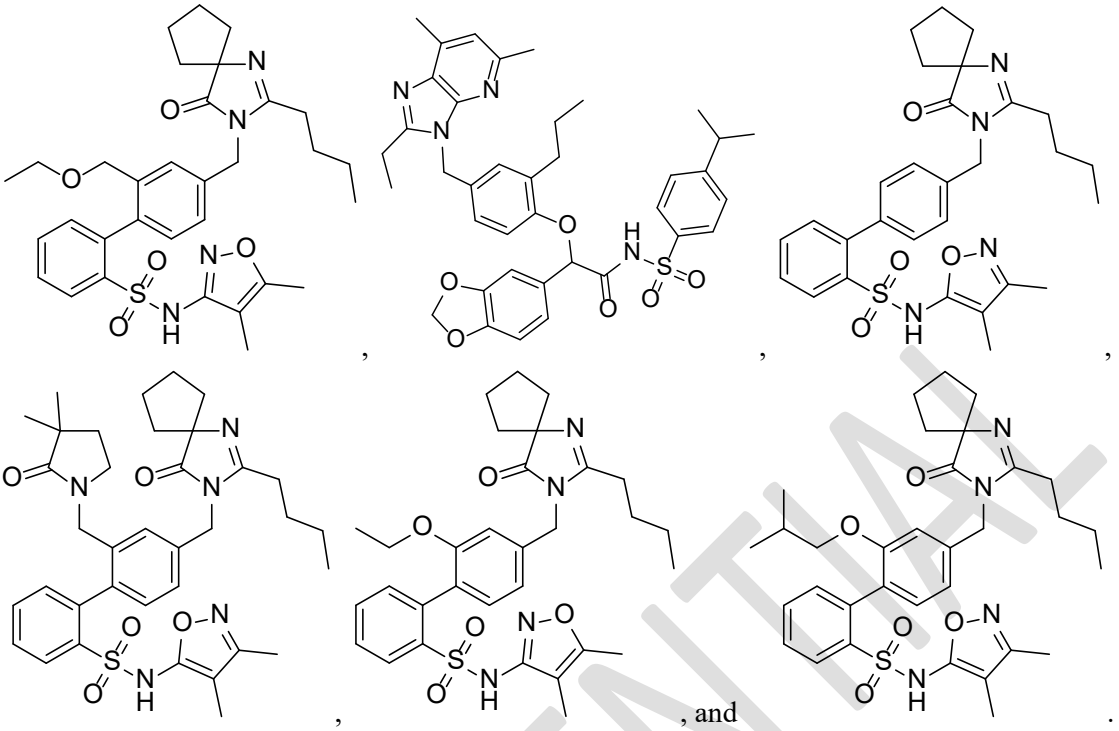
[0044] "Idiopathic pulmonary fibrosis" or "IPF" refers to a chronic, progressive fibrosing interstitial pneumonia of the lungs of unknown cause.

Dual-Acting Angiotensin and Endothelin Receptor Antagonists (DARAs)

[0045] Dual-acting angiotensin and endothelin receptor antagonists (DARAs) are a class of compounds that contain moieties that act separately as antagonists for both angiotensin receptors and endothelin receptors. The fibrotic process is the result of an aberrant response to injury. The process generally proceeds through 3 steps: 1) an initial injury, 2) an inflammation phase, and 3) a remodeling step, which includes the synthesis and deposition of extracellular matrix components by myofibroblasts. Myofibroblasts have been shown to be able to derive from several cell types, including resident fibroblasts, circulating fibroblasts, epithelial/endothelial cells undergoing epithelial/endothelial-to-mesenchymal transition, EMT/EndoMT, vascular pericytes, or hepatic stellate cells. Endothelin A receptor specifically, and not the endothelin B receptor, mediates TGF-β expression, fibroblast proliferation and phenotypic transition, and interstitial lung fibrosis, while also activating phagocytes to induce TNF and IL-1-mediated inflammation. Similarly, angiotensin II receptor type 1 promotes inflammation and fibrosis, in contrast to the action of angiotensin II receptor type 2 and other angiotensin family receptors. The selective roles of the endothelin A and angiotensin II type I receptors that oppose the roles of their homologous isoforms provides an explanation for why pan-endothelin receptor or pan-angiotensin receptor inhibitors have not succeeded as antifibrotic IPF therapies, and conversely, why the selective combination of EDNRA and AGTR1 antagonism is a novel therapeutic approach for the treatment of IPF.

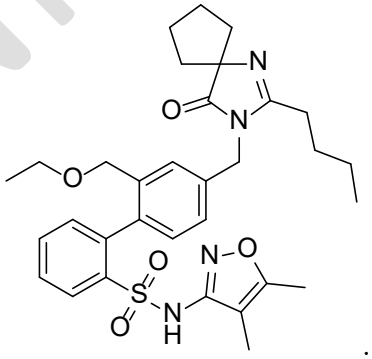
[0046] DARAs are described in at least U.S. Pat. Nos 6,638,937, 6,835,741, and 6,852,745, and published WIPO application WO 2001/44239. Examples of DARAs include, but are not limited to, sparsentan (4'-((2-butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl)-N-(4,5-dimethylisoxazol-3-yl)-2'-(ethoxymethyl)-[1,1'-biphenyl]-2-sulfonamide), Merck (L-746072) (2-(benzo[d][1,3]dioxol-5-yl)-2-(4-((2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl)-2-propylphenoxy)-N-((4-isopropylphenyl)sulfonyl)acetamide), 4'-((2-butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl)-N-(3,4-dimethylisoxazol-5-yl)-[1,1'-biphenyl]-2-sulfonamide, 4'-((2-butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl)-2'-((3,3-dimethyl-2-oxopyrrolidin-1-yl)methyl)-N-(3,4-dimethylisoxazol-5-yl)-[1,1'-biphenyl]-2-sulfonamide, 4'-((2-butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl)-N-(4,5-dimethylisoxazol-3-yl)-2'-ethoxy-[1,1'-biphenyl]-2-sulfonamide, and 4'-((2-butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl)-N-(3,4-dimethylisoxazol-5-yl)-2'-isobutoxy-[1,1'-biphenyl]-2-sulfonamide, and have the following structures:

CONFIDENTIAL



Sparsentan and Compositions Thereof

[0047] In one embodiment, the DARA is sparsentan. Sparsentan is described in U.S. Pat. Nos 6,638,937, 6,835,741 and 6,852,745, and published WIPO application WO 2001/44239. The chemical name of sparsentan is 4'-((2-butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl)-N-(4,5-dimethylisoxazol-3-yl)-2'-(ethoxymethyl)-[1,1'-biphenyl]-2-sulfonamide, and the compound has the following structure:



[0048] The synthesis of sparsentan is known in the art. Sparsentan is also commercially available.

[0049] In some embodiments provided herein, sparsentan is administered as an amorphous solid dispersion. In some embodiments, the amorphous solid is dispersed in a pharmaceutically acceptable polymer matrix. In some embodiments, the pharmaceutically acceptable polymer matrix is selected from

CONFIDENTIAL

hydroxypropyl methylcellulose (hypromellose), hydroxypropyl methylcellulose for HME, hypromellose acetate succinate LG, hypromellose acetate succinate MG, hypromellose acetate succinate HG, hypromellose acetate succinate 716, hypromellose acetate succinate 912, hypromellose acetate succinate 126, polyvinylpyrrolidone / vinyl acetate copolymer, and polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer. In some embodiments, the weight ratio of said amorphous solid sparsentan to said pharmaceutically acceptable polymer matrix is at least 95:5, 90:10, 85:15, 80:20, 75:25, 70:30, 65:35, 60:40, 55:45, 50:50, 45:55, 40:60, 35:65, 30:70, or 25:75. Further description of amorphous solid dispersions of sparsentan can be found in WO 2020/132594, which is incorporated herein by reference.

[0050] Also provided herein, in some embodiments, are pharmaceutical compositions that comprise compounds as described herein, and one or more pharmaceutically acceptable vehicles selected from carriers, adjuvants, and excipients.

[0051] Suitable pharmaceutically acceptable vehicles may include, for example, inert solid diluents and fillers, diluents, including sterile aqueous solution and various organic solvents, permeation enhancers, solubilizers and adjuvants. Such compositions are prepared in a manner well known in the pharmaceutical art. *See, e.g.*, Remington's Pharmaceutical Sciences, Mace Publishing Co., Philadelphia, Pa. 17th Ed. (1985); and Modern Pharmaceutics, Marcel Dekker, Inc. 3rd Ed. (G.S. Banker & C.T. Rhodes, Eds.).

[0052] The pharmaceutical compositions may be administered in either single or multiple doses. The pharmaceutical composition may be administered by various methods including, for example, rectal, buccal, intranasal, and transdermal routes. In certain embodiments, the pharmaceutical composition may be administered by intra-arterial injection, intravenously, intraperitoneally, parenterally, intramuscularly, subcutaneously, orally, topically, or as an inhalant.

[0053] One mode for administration is parenteral, for example, by injection. The forms in which the pharmaceutical compositions described herein may be incorporated for administration by injection include, for example, aqueous or oil suspensions, or emulsions, with sesame oil, corn oil, cottonseed oil, or peanut oil, as well as elixirs, mannitol, dextrose, or a sterile aqueous solution, and similar pharmaceutical vehicles.

[0054] Oral administration may be another route for administration of the compounds described herein. Administration may be via, for example, capsule or enteric coated tablets. In making the pharmaceutical compositions that include at least one compound described herein, the active ingredient is usually diluted by an excipient and/or enclosed within such a carrier that can be in the form of a capsule, sachet, paper or other container. When the excipient serves as a diluent, it can be in the form of a solid, semi-solid, or liquid material, which acts as a vehicle, carrier or medium for the active ingredient. Thus, the compositions can be in the form of tablets, pills, powders, lozenges, sachets, cachets, elixirs, suspensions, emulsions, solutions,

CONFIDENTIAL

syrups, aerosols (as a solid or in a liquid medium), ointments containing, for example, up to 10% by weight of the active compound, soft and hard gelatin capsules, sterile injectable solutions, and sterile packaged powders.

[0055] Some examples of suitable excipients include lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate, alginates, tragacanth, gelatin, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidone, cellulose, sterile water, syrup, and methyl cellulose. The formulations can additionally include lubricating agents such as talc, magnesium stearate, and mineral oil; wetting agents; emulsifying and suspending agents; preserving agents such as methyl and propylhydroxy-benzoates; sweetening agents; and flavoring agents.

[0056] The compositions that include at least one compound described herein can be formulated so as to provide quick, sustained or delayed release of the active ingredient after administration to the subject by employing procedures known in the art. Controlled release drug delivery systems for oral administration include osmotic pump systems and dissolutional systems containing polymer-coated reservoirs or drug-polymer matrix formulations. Examples of controlled release systems are given in U.S. Patent Nos. 3,845,770; 4,326,525; 4,902,514; and 5,616,345. Another formulation for use in the methods disclosed herein employ transdermal delivery devices ("patches"). Such transdermal patches may be used to provide continuous or discontinuous infusion of the compounds described herein in controlled amounts. The construction and use of transdermal patches for the delivery of pharmaceutical agents is well known in the art. *See, e.g.*, U.S. Patent Nos. 5,023,252, 4,992,445 and 5,001,139. Such patches may be constructed for continuous, pulsatile, or on demand delivery of pharmaceutical agents.

[0057] For preparing solid compositions such as tablets, the principal active ingredient may be mixed with a pharmaceutical excipient to form a solid preformulation composition containing a homogeneous mixture of a compound described herein. When referring to these preformulation compositions as homogeneous, the active ingredient may be dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules.

[0058] The tablets or pills of the compounds described herein may be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action, or to protect from the acid conditions of the stomach. For example, the tablet or pill can include an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer that serves to resist disintegration in the stomach and permit the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or

CONFIDENTIAL

coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol, and cellulose acetate.

[0059] Compositions for inhalation or insufflation may include solutions and suspensions in pharmaceutically acceptable, aqueous or organic solvents, or mixtures thereof, and powders. The liquid or solid compositions may contain suitable pharmaceutically acceptable excipients as described herein. In some embodiments, the compositions are administered by the oral or nasal respiratory route for local or systemic effect. In other embodiments, compositions in pharmaceutically acceptable solvents may be nebulized by use of inert gases. Nebulized solutions may be inhaled directly from the nebulizing device or the nebulizing device may be attached to a facemask tent, or intermittent positive pressure breathing machine. Solution, suspension, or powder compositions may be administered, preferably orally or nasally, from devices that deliver the formulation in an appropriate manner.

Methods of Treatment

[0060] Provided herein are methods of treating idiopathic pulmonary fibrosis (IPF), comprising administering a therapeutically effective amount of a dual-acting angiotensin and endothelin receptor antagonist (DARA), to a patient in need thereof. In some embodiments, the dual-acting angiotensin and endothelin receptor antagonist is sparsentan.

[0061] It is contemplated that in treating patients with a DARA agent, certain side effects associated with known therapy may be avoided. For example, diarrhea, gastrointestinal distress, nausea, and photosensitivity like adverse events are not reported with approved endothelin receptor antagonists, and diarrhea and dyspepsia are infrequently reported adverse drug reactions associated with approved angiotensin antagonists. Thus in one embodiment is provided methods of treating idiopathic pulmonary fibrosis in a patient in need thereof, comprising administering sparsentan and having reduced side effects selected from diarrhea, gastrointestinal distress, nausea, photosensitivity, and combinations thereof. This reduction is compared to current IPF therapies, e.g. nintedanib.

[0062] Also provided herein are methods of treating idiopathic pulmonary fibrosis, comprising administering a composition, comprising a therapeutically effective amount of a dual-acting angiotensin and endothelin receptor antagonist (DARA) and a pharmaceutically acceptable carrier, to a patient in need thereof.

[0063] In some embodiments, the therapeutically effective amount of a dual-acting angiotensin and endothelin receptor antagonist treats idiopathic pulmonary fibrosis in a patient in need thereof by suppressing lung epithelial inflammation and fibrosis.

CONFIDENTIAL

[0064] In some embodiments, the therapeutically effective amount of a dual-acting angiotensin and endothelin receptor antagonist treats idiopathic pulmonary fibrosis in a patient in need thereof by suppressing lung myofibroblast phenotypic transition.

[0065] In some embodiments, the patient is 50 years of age or older. In some embodiments, the patient is less than 50 years of age.

[0066] In some embodiments, the patient is a smoker. In some embodiments, the patient is not a smoker.

[0067] In some embodiments, the patient also suffers from gastroesophageal reflux disease (GERD). In some embodiments, the patient does not also suffer from gastroesophageal reflux disease.

[0068] In some embodiments, the patient requires supplemental oxygen. In some embodiments, the patient does not require supplemental oxygen.

[0069] In some embodiments, the patient has a genetic mutation in the MUC5B, TERT, TERC, RTEL1, PARN, SFTPC, or SFTPA2 genes.

[0070] In some embodiments, the patient has a genetic mutation in the MUC5B gene. In some embodiments, the patient has a genetic mutation in the TERT gene. In some embodiments, the patient has a genetic mutation in the TERC gene. In some embodiments, the patient has a genetic mutation in the RTEL1 gene. In some embodiments, the patient has a genetic mutation in the PARN gene. In some embodiments, the patient has a genetic mutation in the SFTPC gene. In some embodiments, the patient has a genetic mutation in the SFTPA2 gene. In some embodiments, the patient has a genetic mutation in more than one gene, said gene selected from the MUC5B, TERT, TERC, RTEL1, PARN, SFTPC, and SFTPA2 genes.

[0071] In some embodiments, the therapeutically effective amount of the dual-acting angiotensin and endothelin receptor antagonist is administered once daily. In some embodiments, the therapeutically effective amount of the dual-acting angiotensin and endothelin receptor antagonist is administered over two doses in a day.

[0072] In some embodiments, the therapeutically effective amount of the dual-acting angiotensin and endothelin receptor antagonist is formulated for oral administration. In some embodiments, the therapeutically effective amount of the dual-acting angiotensin and endothelin receptor antagonist is in tablet form or capsule form. In some embodiments, the therapeutically effective amount of the dual-acting angiotensin and endothelin receptor antagonist is formulated as an amorphous solid dispersion.

[0073] In some embodiments, the therapeutically effective amount of the dual-acting angiotensin and endothelin receptor antagonist is formulated for parenteral administration.

CONFIDENTIAL

[0074] In some embodiments, the therapeutically effective amount of the dual-acting angiotensin and endothelin receptor antagonist is formulated for inhalation.

[0075] In some embodiments, the dual-acting angiotensin and endothelin receptor antagonist is sparsentan or a pharmaceutically acceptable salt thereof.

[0076] In some embodiments, the therapeutically effective amount of sparsentan is about 50 mg/day to about 1000 mg/day. In some embodiments, the therapeutically effective amount of sparsentan is about 100 mg/day to about 900 mg/day. In some embodiments, the therapeutically effective amount of sparsentan is about 200 mg/day to about 800 mg/day. In some embodiments, the therapeutically effective amount of sparsentan is about 400 mg/day to about 600 mg/day.

[0077] In some embodiments, the therapeutically effective amount of sparsentan is about 200 mg/day. In some embodiments, the therapeutically effective amount of sparsentan is about 400 mg/day. In some embodiments, the therapeutically effective amount of sparsentan is about 600 mg/day. In some embodiments, the therapeutically effective amount of sparsentan is about 800 mg/day.

[0078] In some embodiments, sparsentan is dosed at about 400 mg/day to a patient in need thereof, in order to treat idiopathic pulmonary fibrosis, while reducing the occurrence of at least one known side effect of currently known IPF therapies, including, but not limited to, diarrhea, gastrointestinal distress, nausea, disinterest in eating, and photosensitivity.

[0079] In some embodiments, methods provided herein further comprise administering one or more of an additional therapeutic agent. In some embodiments, the additional therapeutic agent is an anti-inflammatory agent.

[0080] In some embodiments, the anti-inflammatory agent is a corticosteroid, such as beclomethasone, betamethasone, budesonide, clobetasol, flunisolide, fluocinolone, fluocinonide, fluticasone, halobetasol, hydrocortisone, methylprednisone, mometasone, prednisolone, prednisone, and triamcinolone. In some embodiments, the anti-inflammatory agent is a non-steroidal anti-inflammatory (NSAIDs), such as a non-selective COX inhibitor or a selective COX-2 inhibitor. Non-selective COX inhibitors include, but are not limited to, salicylic acid derivates (e.g., aspirin, sodium salicylates, choline magnesium trisalicylate, salsalate, diflunisal, sulfasalazine, mesalamine, and olsalazine), para-aminophenol derivatives (e.g., acetaminophen), indole and indene acetic acids (e.g., tolmetin, diclofenac, and ketorolac), heteroaryl acetic acids (e.g., flurbiprofen, ketoprofen, fenprofen, ibuprofen, naproxen, and oxaprozin), anthranilic acids or fenamates (e.g., mefenamic acid and meclofenamic acid), enolic acids (e.g., piroxicam and meloxicam), and alkanones (e.g.,

CONFIDENTIAL

nabumetone). Selective COX-2 inhibitors include, but are not limited to, diaryl-substituted pyrazoles (e.g., celecoxib), indole acetic acids (e.g., etodolac), and sulfonanilides (e.g., nimesulide).

[0081] In some embodiments, the additional therapeutic agent is an immunosuppressive agent. Non-limiting examples of immunosuppressive agents include methotrexate, cyclophosphamide, mizoribine, chlorambucil, cyclosporine, tacrolimus, mycophenolate mofetil, azathioprine, sirolimus, deoxyspergualin, leflunomide, and its malononitriloamide analogs.

[0082] It is understood that modifications which do not substantially affect the activity of the various embodiments of this disclosure are also included within the definition of the disclosure provided herein. Accordingly, the following examples are intended to illustrate but not limit the present disclosure.

EXAMPLES

Example 1:

[0083] The following examples provide an illustrative, non-limiting, procedure that may be utilized when determining the degree of activity of a compound as a dual-acting angiotensin and endothelin receptor antagonist.

$ET_{A/B}$ Attached Cell Binding Assay

[0084] CHO-K1 cells expressing either the human endothelin A or endothelin B receptor are cultured in Ham's F12 media (Gibco/BRL, Grand Island, N.Y.) with 10% fetal bovine serum (Hyclone), supplemented with 300 µg/mL Geneticin (G-418 Gibco BRL Products, Grand Island, N.Y.) and maintained at 37° C with 5% CO_2 in a humidified incubator. Twenty four hours prior to assay, the cells are treated with 0.25% trypsin-EDTA and are seeded in Falcon, 96 well tissue culture plates at a density of 1.8 x 10^4 cells/well (the monolayer should reach 80-90% confluency by the day of assay).

[0085] In the attached cell assay, culture media is aspirated from each well and the monolayers are washed with 50 µL of PBS (Mg^{++}, Ca^{++} free). The binding assay is performed in a total volume of 125 µL consisting of assay buffer (50 mM Tris, pH 7.4, including 1% BSA, and 2 µM phosphoramidon), and 25 µL of either 500 nM ET-1 (to define nonspecific binding) or competing compound. The reaction is initiated with the addition of 25 µL of 0.25 nM [^{125}I]-ET-1 (New England Nuclear). Incubation is carried out with gentle orbital shaking, at 4° C, reaching equilibrium at 4 hours. The reaction is terminated by aspiration of the reaction buffer and two subsequent washes with cold PBS (Mg^{++}, Ca^{++} free). The cells are dissociated by the addition of 100 µL of 0.5N NaOH followed by incubation for 40 minutes. Samples are then transferred from

CONFIDENTIAL

the 96 well format into tubes for counting in a Cobra gamma counter (Packard). Data is analyzed with curve fitting software by Sigma plot.

RASMC Binding Assay

[0086] Assays are conducted in a total volume of 250 µL in 96 well microtitre plates. The incubation mixture contains 50 µL [125]I-Sar-Ile-Angiotensin II (0.2 nM), 25 µL of compound dissolved in DMSO, or angiotensin II (1 µM) to define non-specific binding. Binding to rat aortic smooth muscle cells (RASMCs) is conducted in RPMI media (Gibco BRL Products, Grand Island, N.Y.) containing 0.1% BSA for 2 hours at room temperature with continuous shaking. Unbound radioligand is washed from the wells. The RASMCs with bound radioligand are lysed with 1% Triton X and 0.1% BSA in distilled water for 15 minutes at room temperature with continuous shaking. The solution in each well is transferred to tubes and placed in a gamma counter.

[0087] Compounds within the scope of this invention include compounds that have an IC_{50} concentration of less than 100 micromolar versus either or both [125]I-Sar-Ile-Angiotensin II or [^{125}I]-ET-1, ideally against both ligands. Preferred compounds within the scope of this invention are compounds that have an IC_{50} concentration of less than 5 micromolar versus either or both [125]I-Sar-Ile-Angiotensin II or [^{125}I]-ET-1, ideally against both ligands. More preferred compounds within the scope of this invention are compounds that have an IC_{50} concentration of less than 1 micromolar versus either or both [125]I-Sar-Ile-Angiotensin II or [^{125}I]-ET-1, ideally against both ligands.

Example 2:

[0088] Pulmonary fibrosis was induced in C57BL/6 male mice test groups (group size, n=12) by oropharyngeal aspiration of 75 µL of bleomycin and test agent dosing was begun. The administration of bleomycin also leads to infiltration of lymphocytes and neutrophils in the test subjects' lung tissue, indicative of inflammation. Test agents were administered orally to the test groups once-daily for 21 days. Sparsentan was dosed at 80 mg/kg daily. The reference group received twice-daily oral dosing of nintedanib, with 8 hours between dosage administrations, in a total dose of 60 mg/kg daily. Body weight measurements were performed 3x weekly, beginning on Day 0, and continued during the in-life period for the test groups until Day 21. Daily body weight change for each animal was calculated in comparison to the initial body weight on Day 0. A significant loss in body weight was found after bleomycin administration and remained until study Day 10. A significant decrease in body weight is an expected indicator of disease for this model. On day 21, test groups were euthanized and bronchoalveolar lavage fluid (BALF) and lungs were collected for examination. Lungs were inflated and fixed with formalin for histological analyses. The sparsentan test group

CONFIDENTIAL

was compared to the negative control group (vehicle only) and positive control group (nintedanib treatment) using one-way ANOVA, followed by Dunnett's multiple comparisons. The results are presented in FIG. 1.

[0089] Mice administered sparsentan maintained body weight over the course of treatment better than those administered nintedanib, showing excellent treatment tolerability, as can be seen in FIG. 1. The test group administered only oral gavage vehicle also showed significant beneficial effects on body weight loss when compared to the disease only group, due to DMSO in vehicle formulation.

[0090] Collected lung tissue from the sacrificed test groups described above was stained with Masson's Trichrome for the presence of collagen. Stained tissues were examined microscopically and were scored for collagen level. Mice treated with sparsentan exhibited a significant reduction in collagen staining intensity in lung tissue, comparable to those treated with nintedanib, indicating a significant inhibition ($p < 0.05$) of pulmonary fibrosis compared to those receiving no treatment, as can be seen in FIG. 2.

[0091] Similarly, collected lung tissue from the sacrificed test groups described above was stained with H&E and examined microscopically, to determine a score for inflammation and cell infiltration. Histologic lung samples were assessed via a modified Ashcroft grading system presented in Table 1.

Table 1

Modified Ashcroft Score	
0	**Alveolar septae**: No fibrotic burden **Lung structure**: Normal
1	**Alveolar septae**: Isolated gentle fibrotic changes **Lung structure**: Alveoli partially enlarged and rarefied, but no fibrotic masses present
2	**Alveolar septae**: Clear fibrotic changes with knot-like formation, but not connected to each other **Lung structure**: Alveoli partially enlarged and rarefied, but no fibrotic masses present
3	**Alveolar septae**: Contiguous fibrotic walls, predominately in whole microscopic fields **Lung structure**: Alveoli partially enlarged and rarefied, but no fibrotic masses present
4	**Alveolar septae**: Variable **Lung structure**: Single fibrotic masses (≤10% of microscopic field)
5	**Alveolar septae**: Variable

CONFIDENTIAL

	Lung structure: Confluent fibrotic masses (>10% and ≤50% of microscopic field at 40x). Lung structure severely damaged but still preserved
6	**Alveolar septae**: Variable, mostly not existent **Lung structure**: Large contiguous fibrotic masses (>50% of microscopic field at 40x). Lung architecture mostly not preserved
7	**Alveolar septae**: Non-existent **Lung structure**: Alveoli nearly obliterated with fibrous masses but still up to five air bubbles
8	**Alveolar septae**: Non-existent **Lung structure**: Microscopic field with complete obliteration with fibrotic masses

[0092] Mice treated with sparsentan exhibited lower lung tissue infiltration of neutrophils (FIG. 3) and comparable lung tissue infiltration of lymphocytes (FIG. 4), when compared to those administered nintedanib, indicating a decrease in inflammation compared with the untreated control group.

[0093] TGF-β is widely recognized as a core pathway of fibrosis, so inhibition of TGF-β signaling may offer the potential for antifibrotic therapies. Oral aspiration of bleomycin elevated the level of TGF-β in the bronchoalveolar lavage fluid (BALF) collected from the lungs of the euthanized test groups. Decreased levels of TGF-β were observed in mice treated with nintedanib and sparsentan, as compared to the untreated and vehicle treated animals, as can be seen in FIG. 5.

[0094] Similarly, cells were collected via centrifugation of the sampled BALF, and cell sorting was performed using flow cytometry. Leukocyte ($CD45^+$ cells) infiltration into the lung and/or alveolar tissue is characteristic of inflammation and fibrotic disease. The group treated with sparsentan showed similar $CD45^+$ cell concentrations to the vehicle only and nintedanib test groups, as can be seen in FIG. 6. As can be seen in FIG. 7, macrophage frequency was slightly decreased in the test group dosed with sparsentan, when compared to the other test groups. B-cell populations in the sparsentan treatment group were comparable to those observed in the positive control group (nintedanib treatment), displayed in FIG. 8. T-cell frequency of the sparsentan test group, as seen in FIG. 9, was lower than the untreated and vehicle only test groups. Finally, the sparsentan test group had notably lower neutrophil frequency, as compared with the nintedanib positive control group, as can be seen in FIG. 10.

[0095] Although the invention has been described with reference to the disclosed embodiments, those skilled in the art will readily appreciate that the specific examples and studies detailed above are only

CONFIDENTIAL

illustrative of the invention. It should be understood that various modifications can be made without departing from the spirit of the invention. Accordingly, the invention is limited only by the following claims.

CONFIDENTIAL

WHAT IS CLAIMED:

1. A method for treating idiopathic pulmonary fibrosis (IPF), comprising administering a therapeutically effective amount of a dual-acting angiotensin and endothelin receptor antagonist (DARA) to a patient in need thereof.

2. A method for treating idiopathic pulmonary fibrosis, comprising administering a composition, comprising a therapeutically effective amount of a dual-acting angiotensin and endothelin receptor antagonist and a pharmaceutically acceptable carrier, to a patient in need thereof.

3. The method of any one of claims 1-2, wherein the therapeutically effective amount of the dual-acting angiotensin and endothelin receptor antagonist is formulated for oral administration.

4. The method of any one of claims 1-2, wherein the therapeutically effective amount of the dual-acting angiotensin and endothelin receptor antagonist is in tablet form or capsule form.

5. The method of any one of claims 1-2, wherein the therapeutically effective amount of the dual-acting angiotensin and endothelin receptor antagonist is formulated for parenteral administration.

6. The method of any one of claims 3-5, wherein the therapeutically effective amount of the dual-acting angiotensin and endothelin receptor antagonist is administered once daily.

7. The method of any one of claims 1-2, wherein said administration of a therapeutically effective amount of a dual-acting angiotensin and endothelin receptor antagonist treats idiopathic pulmonary fibrosis in a patient in need thereof while reducing the occurrence of at least one known side effect of currently known IPF therapies, including, but not limited to, diarrhea, gastrointestinal distress, nausea, disinterest in eating, and photosensitivity.

8. The method of any one of claims 1-2, wherein said administration of a therapeutically effective amount of a dual-acting angiotensin and endothelin receptor antagonist treats idiopathic pulmonary fibrosis in a patient in need thereof by suppressing lung epithelial inflammation and fibrosis.

9. The method of any one of claims 1-2, wherein said administration of a therapeutically effective amount of a dual-acting angiotensin and endothelin receptor antagonist treats idiopathic pulmonary fibrosis in a patient in need thereof by suppressing lung myofibroblast phenotypic transition.

10. The method of any one of claims 1-2, wherein said patient has a genetic mutation in the MUC5B, TERT, TERC, RTEL1, PARN, SFTPC, or SFTPA2 genes.

CONFIDENTIAL

11. The method of claim 10, wherein the patient has a genetic mutation in the MUC5B gene.

12. The method of claim 10, wherein the patient has a genetic mutation in the TERT gene.

13. The method of claim 10, wherein the patient has a genetic mutation in the TERC gene.

14. The method of claim 10, wherein the patient has a genetic mutation in the RTEL1 gene.

15. The method of claim 10, wherein the patient has a genetic mutation in the PARN gene.

16. The method of claim 10, wherein the patient has a genetic mutation in the SFTPC gene.

17. The method of claim 10, wherein the patient has a genetic mutation in the SFTPA2 gene.

18. The method of any one of claims 1-2, wherein said patient is 50 years of age or older.

19. The method of any one of claims 1-2, wherein said patient is a smoker.

20. The method of any one of claims 1-2, wherein said patient also suffers from gastroesophageal reflux disease.

21. The method of any one of the preceding claims, wherein the dual-acting angiotensin and endothelin receptor antagonist is sparsentan, or a pharmaceutically acceptable salt thereof.

22. The method of any one of the preceding claims, further comprising administering one or more of an additional therapeutic agent.

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ABSTRACT

Provided herein are formulations comprising a therapeutically effective amount of sparsentan and methods of treating idiopathic pulmonary fibrosis (IPF) by the administration of said formulations.

CONFIDENTIAL