METHODS FOR TREATING IDIOPATHIC PULMONARY FIBROSIS AND ASSOCIATED COMPLICATIONS

Abstract: Methods are provided for inhibiting development of pulmonary hypertension (PH) and/or for improving or inhibiting decline in exercise capacity in a subject having idiopathic pulmonary fibrosis (IPF), comprising administering a therapeutically effective amount of a selective ETA receptor antagonist to the subject. In an embodiment, the method further comprises administering at least one diuretic to the subject. Further provided is a method for treating IPF in a subject, comprising (a) diagnosing IPF without surgical lung biopsy; and (b) if IPF is so diagnosed, administering to the subject a therapeutically effective amount of a selective ETA receptor antagonist, wherein said administration is initiated not more than about 2 years after said diagnosis. Still further provided is a method for improving or inhibiting decline in pulmonary function in a subject having IPF and PH, comprising administering a therapeutically effective amount of an endothelin receptor antagonist to the subject.
METHODS FOR TREATING IDIOPATHIC PULMONARY FIBROSIS AND ASSOCIATED COMPLICATIONS

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. provisional application serial no. 61/108,956 filed October 28, 2008. The entire disclosure of the application is hereby incorporated by reference.

FIELD OF THE INVENTION

[0002] The present invention relates to methods useful for treating idiopathic pulmonary fibrosis (IPF) and/or for inhibiting development of pulmonary hypertension (PH) in IPF patients.

BACKGROUND OF THE INVENTION

[0003] IPF is one of a class of conditions collectively referred to as interstitial lung disease. IPF is a chronic, fibrosing lung disease of unknown etiology that is associated with the histological appearance of usual interstitial pneumonia (UIP). Also termed cryptogenic fibrosing alveolitis, IPF is a clinicopathological syndrome characterized by cough, exertional dyspnea, basilar crackles, a restrictive defect on pulmonary function tests, honeycombing on high-resolution, thin-section computed tomographic (HRCT) scans and the histological diagnosis of UIP on lung biopsy. IPF is a progressive, fatal disease that at present lacks effective treatment.

[0004] Depending upon the criteria used for identification of IPF patients, it is estimated that approximately 29,000 to 89,000 persons in the U.S. have been diagnosed with IPF. The course is usually indolent, but relentless, as most patients die of progressive respiratory failure within 3-8 years of the onset of symptoms. To date, there is no approved therapy for treatment of IPF.

[0005] Uguccioni et al. (1995) J. Clin. Pathol. 48:330-334 report their study on endothelin-1 plasma concentrations in IPF patients and normal controls. They found increased endothelin-1 concentrations in plasma and in the lung tissue of a proportion of patients with IPF.

[0006] Nathan et al. (2007) Am. J. Respir. Crit. Care Med. 175:875-880 mention that "[t]here is a growing appreciation for the role of interceding pulmonary hypertension (PH) in
the course of many diffuse parenchymal lung disorders, including IPF.” According to Nathan et al.’s survey, PH complicating the course of patients with IPF occurs in 32 to 85% of patients. ET-I is mentioned as a candidate molecule in the pathogenesis of IPF-associated PH.

Patel et al. (2007) *Chest* 132:998-1006 discuss various topics on PH in IPF including potential therapies for PH in IPF. With regard to use of ET-I receptor antagonists, the authors mention that the efficacy of this approach is unclear in view of results from a clinical study on bosentan, a dual endothelin A/endothelin B (ET$_A$/ET$_B$) receptor antagonist.

Indeed, clinical trials conducted on IPF have been highly variable in outcome. The study titled "Bosentan Use in Interstitial Lung Disease" (BUILD-I) was a Phase 3, randomized, placebo-controlled study to evaluate efficacy and safety of bosentan in patients with IPF (www.clinicaltrials.gov/ct2/show/NCT00071461?term=%22build+l%22&rank=1).

International Patent Publication No. WO 2007/119214 of Actelion Pharmaceuticals Ltd. is based in part on the BUILD-I study and notes that efficacy of bosentan was restricted to patients with early-stage IPF. The study reportedly did not show an effect on exercise capacity, the primary endpoint of the study, but was effective on secondary endpoints related to death or disease worsening. The findings with bosentan are said therein to be extrapolatable to an extensive list of other endothelin receptor antagonists including selective ET$_A$ antagonists of which ambrisentan and darusentan are mentioned among many others.

King et al. (2008) *Am. J. Respir. Crit. Care* 177:75-81, in a report of the BUILD-I study, set out to determine effects of bosentan on exercise capacity and time to disease progression in patients with IPF. Patients with IPF received 62.5 mg bosentan by oral administration twice daily (b.i.d.) for 4 weeks, then 125 mg b.i.d. for the remainder of the study, or placebo, for 12 months or longer. The primary efficacy endpoint was change from baseline in exercise capacity, as measured by a modified six-minute-walk test (6MWT). Bosentan reportedly showed no superiority over placebo in six-minute-walk distance (6MWD) up to Month 12. A trend in favor of bosentan over placebo was observed in the secondary endpoint of time to death or disease progression; this trend was said to be more pronounced in a patient subgroup diagnosed using surgical lung biopsy. Changes from baseline up to Month 12 in assessments of dyspnea and quality of life also reportedly favored treatment with bosentan.
[0011] Ambrisentan is a non-sulfonamide, propanoic acid-class endothelin receptor antagonist with high affinity (Ki = 0.012 ± 0.004 nM) for ET$_A$ and a high degree of ET$_A$/ET$_B$ selectivity (4703 ± 625 fold). See, for example, Greene et al (2006) J. Am. Coll. Cardiol. 47:307A.

[0012] Ambrisentan is known to be useful in treatment of pulmonary arterial hypertension (PAH). For example, Rubin et al. (2005) Future Cardiol. 1(4):1-8, in a PAH study, reported improvement of mean 6MWD for all patients after 12 weeks of ambrisentan treatment, with a mean increase from baseline of 36 m. The authors reported that similar improvements in 6MWD were observed for patients with World Health Organization (WHO) Functional Class II and III symptoms, indicating that the effects of ambrisentan may not be limited by a "ceiling effect" in less advanced pulmonary arterial hypertension (PAH) patients, as has been reported for another selective ET$_A$ antagonist, sitaxsentan. Additionally, the authors reported that clinically meaningful improvements were also seen in Borg dyspnea index (BDI) and WHO functional class.

[0013] Galie et al. (2005) J. Am. Coll. Cardiol. 46(3):529-535 report results of a randomized dose-ranging study examining efficacy and safety of ambrisentan in patients with PAH. The authors report an increase in exercise capacity in patients with idiopathic PAH as well as in patients with PAH due to other etiologies and for patients in WHO Functional Class II as well as those in WHO Functional Class III.

[0014] U.S. Patent Application Publication No. 2008/0139593 of Gerber & Dufton discloses methods for treating pulmonary hypertension conditions such as PAH by administering ambrisentan, wherein, at baseline, time from first diagnosis of the condition is not greater than about 2 years.

[0015] International Patent Publication No. WO 2008/009071 of Messadek mentions methods for improving cardiovascular efficacy of an endothelin receptor antagonist comprising administering a betaine in combination with the endothelin receptor antagonist. IPF is listed among diseases said to be treatable with such a combination. Endothelin receptor antagonists said to be useful in the methods described include selective ET$_A$ antagonists, of which ambrisentan and darusentan are mentioned among others.

[0016] Pulmonary hypertension (PH) is a term covering a variety of conditions including but not limited to PAH. PH is a known complication of interstitial lung disease and is very
common (approximately one quarter of IPF patients awaiting transplantation) in patients with advanced IPF. The overall incidence of PH in IPF is not well established but has been observed in 32-85% of IPF patients. The presence of PH generally indicates a worse prognosis for IPF patients. Often IPF patients with PH are at a stage where they require lung transplantation.

[0017] Since survival in IPF is affected significantly by PH, a therapy to reduce incidence or severity or to delay onset of PH and PH complications, such as reduction in exercise capacity, would be of great benefit to IPF patients. Additionally, therapies for treating IPF itself, particularly therapies offering benefits not known to occur with bosentan treatment, represent a continuing need in the art.

SUMMARY OF THE INVENTION

[0018] There is now provided a method for inhibiting development of PH in a subject having IPF, the method comprising administering a therapeutically effective amount of a selective ET<sub>A</sub> receptor antagonist to the subject, wherein the subject at baseline does not have a diagnosis of PH.

[0019] There is further provided a method for inhibiting development of PH in a subject having IPF, the method comprising administering a therapeutically effective amount of a selective ET<sub>A</sub> receptor antagonist and a therapeutically effective amount of a diuretic to the subject.

[0020] There is still further provided a method for improving, or inhibiting decline in, exercise capacity in a subject having IPF, the method comprising administering to the subject a therapeutically effective amount of a selective ET<sub>A</sub> receptor antagonist, wherein the subject at baseline exhibits a 6MWD not greater than about 450 m.

[0021] There is still further provided a method for treating IPF in a subject, comprising (a) diagnosing IPF without surgical lung biopsy; and (b) if IPF is so diagnosed, administering to the subject a therapeutically effective amount of a selective ET<sub>A</sub> receptor antagonist, wherein said administration is initiated not more than about 2 years after said diagnosis.

[0022] There is still further provided a method for improving, or inhibiting decline in, pulmonary condition in a subject having IPF and PH, the method comprising administering to the subject a therapeutically effective amount of an endothelin receptor antagonist.

[0023] Other embodiments, including particular aspects of the embodiments summarized above, will be evident from the detailed description that follows.
DETAILED DESCRIPTION

[0024] The publications cited individually below contain information related to the present invention and are incorporated in their entirety herein without admission that they constitute prior art to the present invention.

[0025] In various aspects of the present invention, methods are provided for treating IPF and IPF-associated complications. All methods of the invention involve administration of a "selective ET<sub>A</sub> receptor antagonist". As used herein, the term "selective ET<sub>A</sub> receptor antagonist" means an endothelin receptor antagonist exhibiting substantially greater ET<sub>A</sub>/ET<sub>B</sub> selectivity than the dual ET<sub>A</sub>/ET<sub>B</sub> receptor antagonist bosentan. It will be understood that measured ET<sub>A</sub> and ET<sub>B</sub> receptor affinities, and the selectivity factors calculated therefrom, can depend greatly on the particular assay method used, thus a compound having "substantially greater ET<sub>A</sub>/ET<sub>B</sub> selectivity than bosentan" herein exhibits such greater selectivity when compared head-to-head with bosentan by the same assay method. The term "substantially greater" in the present context will be understood by one of skill in the art to mean sufficiently greater to have practical consequences in terms of reduced ET<sub>B</sub> binding at concentrations providing a useful level of ET<sub>A</sub> binding. In various embodiments, ET<sub>A</sub>/ET<sub>B</sub> selectivity is at least about 2 x greater, at least about 3 x greater, at least about 4 x greater or at least about 5 x greater, than that of bosentan measured by the same method.

[0026] A presently preferred assay method for determining ET<sub>A</sub> and ET<sub>B</sub> affinities and ET<sub>A</sub>/ET<sub>B</sub> selectivity is that described in the above-cited Greene et al. (2006) publication, incorporated by reference in its entirety herein. In the Greene method, affinities of endothelin receptor antagonists for ET<sub>A</sub> and ET<sub>B</sub> are measured in the same human tissue preparation. Specifically, <sup>125</sup>I-endothelin-1 receptor binding-cold ligand competition curves are generated in human myocardial membranes prepared from non-failing and failing left ventricles, and cold ligand dissociation constants (Ki values) are determined for ET<sub>A</sub> and ET<sub>B</sub> by computer modeling. Assay conditions include 10 µM Gpp(NH)p (guanylyl-5'-imidodiphosphate) to eliminate high-affinity agonist binding, 18-point competition curves between 1 pM and 100 µM, and a 4-hour incubation period to achieve steady-state binding. Without being bound by theory, it is believed that achieving steady-state binding is particularly relevant to assessing ET<sub>A</sub>/ET<sub>B</sub> selectivity. Full details of the Greene method and results obtained thereby were presented in poster form at an ACC (American College of Cardiology) meeting (Greene et al.}

[0027] Illustratively according to the Greene method, the dual ET_A/ET_B receptor antagonist bosentan exhibits a Ki for ET_A of 0.156 ± 0.051 nM. The selective ET_A receptor antagonist darusentan is similar in this regard (Ki for ET_A of 0.178 ± 0.055 nM); the selective ET_A receptor antagonist ambrisentan has greater affinity as shown by a lower Ki for ET_A of 0.012 ± 0.004 nM; and the selective ET_A receptor antagonist sitaxsentan has somewhat lower affinity as shown by a higher Ki for ET_A of 20.1 ± 5.7 nM. In particular embodiments of the present invention, the selective ET_A receptor antagonist administered, when measured by the Greene method, has a Ki for ET_A not greater than about 50 nM, for example not greater than about 20 nM, not greater than about 10 nM, not greater than about 5 nM, not greater than about 2 nM, not greater than about 1 nM, not greater than about 0.5 nM, not greater than about 0.2 nM or not greater than about 0.1 nM.

[0028] Illustratively according to the Greene method, bosentan exhibits ET_A/ET_B selectivity of 242 ± 49 fold. By contrast, sitaxsentan exhibits ET_A/ET_B selectivity of 893 ± 201 fold (about 3.7 x that of bosentan); darusentan exhibits ET_A/ET_B selectivity of 1181 ± 149 fold (about 4.9 x that of bosentan); and ambrisentan exhibits ET_A/ET_B selectivity of 4703 ± 625 fold (about 19.4 x that of bosentan). It should be understood that the Greene assay for determining ET_A and ET_B affinities is exemplary, and one of ordinary skill in the art may modify the method by using different conditions and materials. For example, ET_A/ET_B selectivity data can be determined with different tissues such as myocardial left ventricular (LV) membranes and Chinese Hamster Ovary (CHO) cell membranes. It was found that the patterns of the ET_A/ET_B selectivity from LV and CHO show the same trend as that of Greene and that the data are useful to identify a selective ET_A receptor antagonist. In other words, it was possible to screen endothelin receptor antagonists having substantially higher ET_A selectivity than mixed ET receptor antagonist such as bosentan.

[0029] In particular embodiments of the present invention, ET_A/ET_B selectivity of the selective ET_A receptor antagonist administered, when measured by the Greene method, is at least about 500 fold, for example at least about 750 fold or at least about 1000 fold.

[0030] Bosentan has been reported to cause drug-related and dose-dependent liver
function test (LFT) abnormalities, specifically elevated serum levels of alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) that can be associated with hepatotoxicity. For example, in the BUILD-I study as reported in the above-cited publication by King et al. (2008), elevations in serum ALT were reported for 20.5% of subjects receiving 125 mg bosentan b.i.d. compared to 0.0% of subjects receiving placebo, and 12% of the bosentan-treated subjects discontinued the study due to abnormal LFTs.

These results are consistent with earlier studies of bosentan in PAH, as indicated on the Tracleer® (bosentan) label approved by the U.S. Food & Drug Administration (FDA) and available at [www.fda.gov/cder/foi/label/2007/021290s0101bl.pdf](http://www.fda.gov/cder/foi/label/2007/021290s0101bl.pdf). The label states that elevations in ALT or AST by \( >3 \times \text{ULN} \) (upper limit of normal) were observed in 12%, and elevations by \( \geq 8 \times \text{ULN} \) in 2%, of patients receiving 125 mg bosentan b.i.d.; in patients receiving 250 mg bosentan b.i.d., incidence of such elevations was 14% and 7% respectively.

By contrast, ambrisentan has been associated with a low incidence of aminotransferase abnormalities. In a 12-week study, the incidence of ALT or AST \( \geq 3 \times \text{ULN} \) for all subjects receiving ambrisentan (0.8%) was lower than for subjects receiving placebo (2.3%). With long-term treatment, the 1-year incidence of ALT or AST \( \geq 3 \times \text{ULN} \) was 2.8% and of ALT or AST \( \geq 8 \times \text{ULN} \) was 2.8%. In addition, ambrisentan was well-tolerated and not associated with aminotransferase abnormalities in subjects with PAH who had previously discontinued sulfonamide \( \text{e.g.,} \) bosentan) therapy due to aminotransferase abnormalities.

Studies in isolated lung fibroblasts suggest that difference in ET\(_A\) and ET\(_B\) effects may exist in systems directly related to IPF. Two hallmarks of lung fibroblast activation are contraction and proliferation. Contractile activity of activated lung fibroblasts is blocked by ET\(_A\) antagonism, but not ET\(_B\) antagonism. In addition, ET-I-induced lung fibroblast proliferation (including MAP kinase pathway activation) is blocked by ET\(_A\) antagonism, but not ET\(_B\) antagonism. Due to the differing physiologic actions of ET\(_A\) and ET\(_B\) receptors, the inventors believe that a selective ET\(_A\) antagonist, \( \text{e.g.,} \) ambrisentan, provides a benefit over a mixed ET\(_A\)/ET\(_B\) antagonist in attenuating lung fibroblast activation. Furthermore, ambrisentan and darusentan may reduce the risk of hepatotoxicity relative to a mixed ET\(_A\)/ET\(_B\) antagonist such as bosentan.

Development of PH in a subject with IPF is associated with diminished longevity or increased mortality, or hastens the time when lung transplantation becomes necessary for
survival. As PH, more particularly PAH, is known to be treatable with a selective ET\textsubscript{A} receptor antagonist such as ambrisentan, a patient presenting with IPF and associated PH could be prescribed a selective ET\textsubscript{A} receptor antagonist to treat both the PH and the underlying IPF. However, it has hitherto been unknown that a patient who at baseline has a diagnosis of IPF but not of PH can benefit from selective ET\textsubscript{A} receptor antagonist therapy not only through treatment of the IPF but through delaying onset of PH and/or slowing progression of PH after onset occurs.

Therefore, one embodiment of the invention provides a method for inhibiting development of PH in a subject having IPF, comprising administering a therapeutically effective amount of a selective ET\textsubscript{A} receptor antagonist to the subject. The subject according to this embodiment is one who at baseline does not have a diagnosis of PH. Thus with respect to PH, at least initial treatment with the selective ET\textsubscript{A} receptor antagonist is in a sense preventive or prophylactic. It will be understood that the terms "preventive" or "prevention" are used herein in their usual medical sense of reducing incidence or risk of an adverse event or delaying onset of an adverse medical condition, and do not imply complete avoidance of such an event or condition.

A "subject having IPF" herein has, in most cases, received a formal diagnosis of IPF, based for example on computed tomography (CT), especially high-resolution computed tomography (HRCT), and/or surgical lung biopsy (SLB). However, in some embodiments the "subject having IPF" has characteristic clinical manifestations of IPF but a formal diagnosis of IPF has not yet been made.

The term "baseline" herein refers to a time immediately prior to commencement of treatment with a selective ET\textsubscript{A} receptor antagonist, e.g., ambrisentan. At baseline, a subject may have clinical manifestation of IPF without formal diagnosis, may have newly received a diagnosis of IPF, or may have received such diagnosis much earlier, for example several weeks, months or even years earlier. It is generally preferable to start therapy according to the present method as soon as possible, for example not later than about 2 years, about 18 months, about 12 months or about 6 months, after diagnosis of IPF.

The term "inhibiting development" with respect to PH includes (1) delaying onset or clinical diagnosis of PH and/or (2) retarding or arresting progression of PH once such onset or clinical diagnosis occurs. Thus in various embodiments treatment with a selective ET\textsubscript{A}
receptor antagonist beginning before diagnosis of PH results in:

- onset or clinical diagnosis of PH later than would otherwise occur; or
- onset of clinical diagnosis of PH no later than would otherwise occur, but slower progression of PH following such onset or clinical diagnosis; or
- both a delay in onset or clinical diagnosis of PH and slower progression of PH following such onset or clinical diagnosis.

[0039] The phrase "clinical diagnosis" with respect to PH means recognition by a physician or clinician of a PH condition, for example PAH, in the subject, by any means whether or not hemodynamic evaluation is conducted to confirm the diagnosis. However, in one embodiment, diagnosis is confirmed hemodynamically, for example in the case of PAH by presence of one or more, more typically two or all three of the following:

(a) mean pulmonary arterial pressure (PAP) not less than about 25 mmHg at rest or not less than about 30 mmHg while exercising;
(b) pulmonary vascular resistance (PVR) not less than about 3 mmHg/liter/minute;
and/or
(c) pulmonary capillary wedge pressure (PCWP) or left ventricle end diastolic pressure (LVEDP) not greater than about 15 mmHg.

[0040] PH conditions, development of which can be inhibited in IPF patients by the present method, include any one or more of the conditions recognized according to the WHO or "Venice 2003" classification. See, for example, Rubin (2004) _Chest_ 126:7-10). These conditions include:

Group 1: Pulmonary arterial hypertension (PAH)

1.1 idiopathic PAH
1.2 familial PAH
1.3 PAH associated with:

1.3.1 collagen vascular disease
1.3.2 congenital systemic-to-pulmonary shunts (including Eisenmenger's syndrome)
1.3.3 portal hypertension
1.3.4 HIV infection
1.3.5 drugs and toxins
1.3.6 other (including thyroid disorders, glycogen storage disease, Gaucher disease, hereditary hemorrhagic telangiectasia, hemoglobinopathies, myeloproliferative disorders, splenectomy)

1.4 PAH associated with significant venous or capillary involvement
   1.4.1 pulmonary veno-occlusive disease (PVOD)
   1.4.2 pulmonary capillary hemangiomatosis (PCH)

1.5 persistent pulmonary hypertension of the newborn

Group 2: Pulmonary hypertension with left heart disease
   2.1 left-sided atrial or ventricular heart disease
   2.2 left-sided valvular heart disease

Group 3: Pulmonary hypertension associated with lung diseases and/or hypoxemia
   3.1 chronic obstructive pulmonary disease (COPD)
   3.2 interstitial lung disease
   3.3 sleep-disordered breathing
   3.4 alveolar hypoventilation disorders
   3.5 chronic exposure to high altitude
   3.6 developmental abnormalities

Group 4: Pulmonary hypertension due to chronic thrombotic and/or embolic disease
   4.1 thromboembolic obstruction of proximal pulmonary arteries
   4.2 thromboembolic obstruction of distal pulmonary arteries
   4.3 non-thrombotic pulmonary embolism (tumor, parasites, foreign material)

Group 5: Miscellaneous (sarcoidosis, histiocytosis X, lymphangiomatosis, compression of pulmonary vessels (adenopathy, tumor, fibrosing mediastinitis)

[0041] Of special interest herein is PH associated with interstitial lung disease (Group 3.2), it being recognized that IPF is one of several conditions classified as a type of interstitial lung disease (ILD).

[0042] In a particular embodiment, the method is useful for delaying onset or clinical diagnosis of PH in a subject having IPF, wherein the subject at baseline does not have a diagnosis of PH.
In another particular embodiment, the method is useful for retarding or arresting progression of PH once onset or clinical diagnosis of PH occurs, wherein the subject at baseline does not have a diagnosis of PH.

In either of these embodiments, the subject at baseline typically has no outward clinical signs of PH, but in some situations it is possible that the subject may have symptoms suggestive of or leading to a diagnosis of PH without such diagnosis having formally been made at baseline.

The present method is also intended to treat IPF- or PH-associated diseases. An example of such diseases includes cor plunomale which is defined by failure of the right side of the heart brought on by long-term high blood pressure in the pulmonary arteries and right ventricle of the heart.

Any PH condition which may develop in the IPF patient can be mild, moderate or severe, as defined for example by WHO functional class, which is a measure of disease severity in patients with PH. The WHO functional classification is an adaptation of the New York Heart Association (NYHA) system and is routinely used to qualitatively assess activity tolerance, for example in monitoring disease progression and response to treatment (Rubin (2004), supra). Four functional classes are recognized in the WHO system:

Class I: PH without resulting limitation of physical activity; ordinary physical activity does not cause undue dyspnea or fatigue, chest pain or near syncope;

Class II: PH resulting in slight limitation of physical activity; patient comfortable at rest; ordinary physical activity causes undue dyspnea or fatigue, chest pain or near syncope;

Class III: PH resulting in marked limitation of physical activity; patient comfortable at rest; less than ordinary activity causes undue dyspnea or fatigue, chest pain or near syncope;

Class IV: PH resulting in inability to carry out any physical activity without symptoms; patient manifests signs of right-heart failure; dyspnea and/or fatigue may be present even at rest; discomfort is increased by any physical activity.

In various embodiments, progression of PH to WHO Class II, Class III or Class IV is retarded or prevented by practice of the present method.
In a particular embodiment, a method for inhibiting development of PH in a subject having IPF, but not having a diagnosis of PH at baseline, comprises administering to the subject a selective ET$_A$ receptor antagonist in an amount effective to maintain one or more hemodynamic parameters indicative of a PH condition at a more normal level than would otherwise be the case; or to lower (thus improve) one or more hemodynamic parameters indicative of a PH condition toward a more normal level.

For example, in one aspect, the selective ET$_A$ receptor antagonist is administered in an amount effective to maintain PAP at a level not greater than about 30 mmHg, for example not greater than about 25 mmHg. In another aspect, the selective ET$_A$ receptor antagonist is administered in an amount effective to maintain PVR at a level not greater than about 3.5 mmHg/1/min, for example not greater than about 3 mmHg/1/min. In yet another aspect, the selective ET$_A$ receptor antagonist is administered in an amount effective to maintain PCWP or LVEDP at a level of at least about 12 mmHg, for example at least about 15 mmHg.

PAP, PVR, PCWP and/or LVEDP can be measured by any suitable procedure, but are preferably measured at rest during a right heart catheterization (RHC) procedure.

In another particular embodiment, a method for inhibiting development of PH in a subject having IPF, but not having a diagnosis of PH at baseline, comprises administering to the subject a selective ET$_A$ receptor antagonist in an amount effective to improve exercise capacity or to inhibit decline in exercise capacity relative to baseline and/or placebo.

Any suitable measure of exercise capacity can be used; a particularly suitable measure is obtained in a walk test over a defined time interval, for example 6 minutes. The 6-minute walk test (6MWT) is a standard procedure which measures distance walked by a subject in 6 minutes, i.e., 6MWD. However, any test equivalent to the 6MWT may be used. An equivalent test is any test which can demonstrate exercise capacity, such as a modified 6MWT in which time, distance or other test parameters are modified.

In various aspects, 6MWD is increased over baseline and/or over placebo by at least about 10 m, for example at least about 20 m or at least about 30 m. In many instances, the present method will be found effective to increase 6MWD by as much as 50 m or even more.

In yet another particular embodiment, a method for inhibiting development of PH in a subject having IPF, but not having a diagnosis of PH at baseline, comprises administering
to the subject a selective ET\textsubscript{A} receptor antagonist in an amount effective to delay onset of PH by comparison with placebo. Onset of PH can mean onset of clinical manifestation of PH with or without formal clinical diagnosis of PH (e.g., by RHC); in one aspect, however, onset is defined by formal clinical diagnosis. As for all parameters where comparison with placebo is required, it will be understood that an "amount effective" to provide a given result, in the present instance a delay in onset of PH, can be determined by one of skill in the art by reviewing results of a placebo-controlled clinical trial.

[0055] In various aspects, onset of PH is delayed by at least about 3 months, for example at least about 6 months or at least about 12 months when compared to placebo. In one aspect, onset of PH is delayed indefinitely, in other words, the subject never develops PH during the entire period of treatment with the selective ET\textsubscript{A} receptor antagonist.

[0056] In yet another particular embodiment, a method for inhibiting development of PH in a subject having IPF, but not having a diagnosis of PH at baseline, comprises administering to the subject a selective ET\textsubscript{A} receptor antagonist in an amount effective to reduce probability of a clinical worsening event (CWE) during the treatment period, by comparison with placebo. In various aspects, a reduction of at least about 25%, for example at least about 50%, at least about 70% or at least about 80%, in probability of a CWE during the treatment period is provided. Reducing probability of a CWE will be understood to be closely related to extending time to clinical worsening, and can be considered another way of expressing the same concept.

[0057] CWEs include death, lung transplantation, hospitalization for PH or IPF, atrial septostomy, initiation of additional PH or IPF therapy or an aggregate of two or more such events. Thus in various aspects, the selective ET\textsubscript{A} receptor antagonist is administered in an amount effective to provide a reduction of at least about 25%, for example at least about 50%, at least about 70% or at least about 80%, in probability of death, lung transplantation, hospitalization for PH or IPF, atrial septostomy and/or initiation of additional PH or IPF therapy during the treatment period, by comparison with placebo.

[0058] In yet another particular embodiment, a method for inhibiting development of PH in a subject having IPF, but not having a diagnosis of PH at baseline, comprises administering to the subject a selective ET\textsubscript{A} receptor antagonist in an amount effective to inhibit worsening of or to ameliorate quality of life of the subject versus baseline and/or placebo, illustratively
as measured by one or more of the health parameters recorded in an SF-36® survey, the St. George's respiratory questionnaire, the Cambridge pulmonary hypertension outcome review (CAMPHOR) or any equivalent survey or questionnaire.

[0059] The SF-36® health survey provides a self-reporting, multi-item scale measuring eight health parameters: physical functioning, role limitations due to physical health problems, bodily pain, general health, vitality (energy and fatigue), social functioning, role limitations due to emotional problems, and mental health (psychological distress and psychological well-being). The survey also provides a physical component summary and a mental component summary. For further detail see, for example, SF-36® Health Survey Update at www.sf-36.org/tools/sf36.shtml.

[0060] Thus, for example, an improvement can be obtained in at least one of the SF-36® physical health-related parameters (physical health, role-physical, bodily pain and/or general health) and/or in at least one of the SF-36® mental health-related parameters (vitality, social functioning, role-emotional and/or mental health). Such an improvement can take the form of an increase of at least 1, for example at least 2 or at least 3 points, on the scale for any one or more parameters, by comparison with baseline or by comparison with placebo.

[0061] The St. George's respiratory questionnaire is a respiratory-specific measure. Thus, for example, an improvement can be obtained in at least one of the respiratory health related parameters of the St George's respiratory questionnaire.

[0062] In yet another particular embodiment, a method for inhibiting development of PH in a subject having IPF, but not having a diagnosis of PH at baseline, comprises administering to the subject a selective ET_A receptor antagonist in an amount effective to improve dyspnea. Dyspnea includes shortness of breath, difficulty in breathing and/or painful breathing. Dyspnea is a primary symptom in IPF patients and worsening dyspnea has been characterized as a component of the clinical course of mild to moderate IPF. Dyspnea can be measured, for example, by the Transitional Dyspnea Index (TDI) or the University of California San Diego Shortness of Breath Questionnaire (USCD SOBQ).

[0063] In any of the above embodiments, the subject can have early-stage IPF. HRCT as well as classical CT, together with pulmonary function tests, are to date the best non-invasive tools for assessing extent of IPF and for delineating its stage of progression. Typically IPF in its earliest stages shows ground-glass attenuation with little or no honeycomb on CT scan.
Ground-glass attenuation corresponds histologically to patchy alveolar septal fibrosis, airspace filling with macrophages with interstitial inflammation. At a later stage, ground-glass will be substituted by more reticular opacities and honeycomb. The latter corresponds to destruction of the lung with dilatation of bronchioles that communicate with proximal airways. Honeycomb lesions tend to enlarge slowly over time. Honeycomb can be semi-quantitated on HRCT as a percentage.

Early-stage IPF can be characterized by presence of zero to about 5% honeycomb on HRCT or CT scans, as well as presence of ground-glass attenuation in one or both lungs, but is not limited to these features. In rare cases HRCT does not show ground-glass attenuation and/or honeycomb and/or reticulation. However, early-stage IPF can also be diagnosed by other usual diagnostic tools, such as but not limited to magnetic resonance imaging (MRI), broncho-alveolar lavage, or lung biopsy for histological assessment (e.g., surgical (SLB), transbronchial, or via mediastinoscopy). Despite low or no honeycomb visible on HRCT scan, honeycomb still may be visible in histological sections. Additionally, early IPF can be diagnosed by cardio-pulmonary exercise test.

Thus, in one aspect, the subject has zero to about 5% honeycomb on HRCT or lung biopsy. In a further aspect, the subject at baseline has greater than about 3.3%, for example about 3.3% to about 5%, honeycomb on HRCT or lung biopsy.

In any of the above embodiments, the subject at baseline can have a clinical diagnosis of IPF wherein the diagnosis is made without SLB, such as by CT or HRCT.

As noted above, the dual ET$_A$/ET$_B$ receptor antagonist bosentan has not demonstrated any benefit for exercise capacity in subjects having IPF. See, for example, the report of the BUILD-I study by King et al. (2008), supra, in which bosentan showed no superiority over placebo in 6MWD. According to one embodiment of the present invention, by contrast, an ET$_A$ receptor antagonist having substantially greater ET$_A$/ET$_B$ selectivity than bosentan, illustratively ambrisentan, is capable of improving, or inhibiting decline in, exercise capacity in a subject having IPF. Thus one embodiment of the invention provides a method for improving, or inhibiting decline in, exercise capacity in a subject having IPF, comprising administering a therapeutically effective amount of a selective ET$_A$ receptor antagonist to the subject. The method of this embodiment has particular benefit for a subject who at baseline exhibits a 6MWD not greater than about 450 m. In various aspects, the subject exhibits at
baseline a 6MWD not greater than about 400 m, for example not greater than about 350 m or not greater than about 300 m.

[0068] The subject according to the present method may or may not have PH at baseline. In one aspect, the subject has PH in association with or as a complicating condition to IPF.

[0069] All relevant aspects discussed above in connection with inhibiting development of PH apply mutatis mutandis to the present embodiment. For example, according to the present embodiment, the subject can have, or develop, PH of any of Classes I, II, II or IV, or can fail to develop PH at all. The selective ET\textsubscript{A} receptor antagonist can be administered in an amount effective to improve, or inhibit decline in, one or more hemodynamic parameters including PAP, PVR, PCWP and/or LVEDP. The selective ET\textsubscript{A} receptor antagonist can be administered in an amount effective to reduce probability of a CWE during the treatment period. The selective ET\textsubscript{A} receptor antagonist can be administered in an amount effective to inhibit worsening of or to ameliorate quality of life. The selective ET\textsubscript{A} receptor antagonist can be administered in an amount effective to improve dyspnea. The subject can illustratively exhibit zero to about 5%, for example about 3.3% to about 5%, honeycomb on HRCT or lung biopsy. The subject at baseline can have a clinical diagnosis of IPF made without SLB, such as by CT or HRCT.

[0070] As noted above, the dual ET\textsubscript{A}/ET\textsubscript{B} receptor antagonist bosentan has not demonstrated any benefit in subjects having IPF diagnosed without SLB. See, for example, the report of the BUILD-I study by King et al. (2008), supra, in which bosentan showed no superiority over placebo in such subjects. According to one embodiment of the present invention, by contrast, an ET\textsubscript{A} receptor antagonist having substantially greater ET\textsubscript{A}/ET\textsubscript{B} selectivity than bosentan, illustratively ambrisentan, is capable of providing benefit, for example in exercise capacity, in hemodynamic parameters, in probability of a CWE, in quality of life and/or in dyspnea, to a subject having IPF diagnosed without SLB.

[0071] Thus one embodiment of the invention provides a method for treating IPF in a subject, comprising

(a) diagnosing IPF without surgical lung biopsy; and
(b) if IPF is so diagnosed, administering to the subject a therapeutically effective amount of a selective ET\textsubscript{A} receptor antagonist.
[0072] The method of this embodiment has particular benefit for the subject if administration of the selective ET<sub>A</sub> receptor antagonist is initiated not more than about 2 years, for example not more than about 18 months, not more than about 12 months, not more than about 6 months or not more than about 3 months, after the diagnosis of IPF.

[0073] Diagnosing IPF "without surgical lung biopsy" in the present context does not rule out later confirmation of the diagnosis by SLB, so long as such later confirmation occurs after initiation of a treatment regimen with a selective ET<sub>A</sub> receptor antagonist according to the present method. However, in one particular embodiment, no SLB is conducted either before or during the period of treatment.

[0074] In another particular embodiment, the subject is judged by a competent physician to be an unsuitable candidate for SLB, for medical or other reasons.

[0075] Wherever possible, diagnostic procedures that are less invasive than SLB are generally favored, and a current trend is evident for more and more diagnoses of IPF being made by such less invasive procedures, including CT, for example HRCT. For this reason, a therapeutic method that is effective for treatment of IPF in subjects diagnosed by procedures other than SLB represents an important advance in the art, especially in view of the disappointing results of the above-referenced BUILD-I study in this regard.

[0076] In a particular embodiment of the present method, diagnosis of IPF is made with the aid of HRCT.

[0077] The subject according to the method of the present embodiment may or may not have PH at baseline. In one aspect, the subject has PH in association with or as a complicating condition to IPF.

[0078] All relevant aspects discussed above in connection with inhibiting development of PH apply mutatis mutandis to the present embodiment. For example, according to the present embodiment, the subject can have, or develop, PH of any of Classes I, II, II or IV, or can fail to develop PH at all. The selective ET<sub>A</sub> receptor antagonist can be administered in an amount effective to improve, or inhibit decline in, one or more hemodynamic parameters including PAP, PVR, PCWP and/or LVEDP. The selective ET<sub>A</sub> receptor antagonist can be administered in an amount effective to reduce probability of a CWE during the treatment period. The selective ET<sub>A</sub> receptor antagonist can be administered in an amount effective to inhibit worsening of or to ameliorate quality of life. The selective ET<sub>A</sub> receptor antagonist
can be administered in an amount effective to improve dyspnea. The subject can illustratively exhibit zero to about 5%, for example about 3.3% to about 5%, honeycomb on HRCT.

[0079] A particularly challenging population for treatment is one wherein the subject at baseline has both IPF and PH, and who therefore has pulmonary function compromised by two serious disorders. The PH in such a subject can be, but is not necessarily, secondary to the IPF. Accordingly there is provided, in a further embodiment of the invention, a method for improving, or inhibiting decline in, pulmonary condition in a subject having IPF and PH comprises administering to the subject a therapeutically effective amount of an endothelin receptor antagonist.

[0080] The term "pulmonary condition" in the present context refers to any measure of pulmonary health or lack thereof as evidenced, for example, by results of a pulmonary function test (PFT) or a test of exercise capacity, or by a dyspnea index such as the BDI (Borg dyspnea index) or TDI (transitional dyspnea index). PFTs that can be used to assess a subject's condition include tests for forced vital capacity (FVC) or diffusing capacity of the lung for carbon monoxide (DLCO), which are standard in the art. Tests of exercise capacity include walking tests such as the 6MWT referred to hereinafore.

[0081] In the method of the present embodiment, any endothelin receptor antagonist can be used, preferably an ET_A receptor antagonist, which can be a dual ET_A/ET_B receptor antagonist such as bosentan or a selective ET_A receptor antagonist such as those mentioned below.

[0082] All relevant aspects discussed above in connection with inhibiting development of PH apply mutatis mutandis to the present embodiment, except that the subject in accordance with the present embodiment has PH as well as IPF at baseline. For example, according to the present embodiment, the subject can have PH of any of Classes I, II, II or IV. The endothelin receptor antagonist can be administered in an amount effective to improve, or inhibit decline in, one or more hemodynamic parameters including PAP, PVR, PCWP and/or LVEDP. The endothelin receptor antagonist can be administered in an amount effective to reduce probability of a CWE during the treatment period. The endothelin receptor antagonist can be administered in an amount effective to inhibit worsening of or to ameliorate quality of life. The endothelin receptor antagonist can be administered in an amount effective to improve dyspnea. The subject can illustratively exhibit zero to about 5%, for example about 3.3% to about 5%, honeycomb on HRCT.
Suitable selective ET<sub>A</sub> receptor antagonists for use in any of the methods provided herein can be identified by one of ordinary skill from literature on such antagonists, based on the disclosure herein, but a non-limiting list of such antagonists includes ambrisentan, atrasentan, avosentan, BMS 193884, BQ-123, CI-1020, clazosentan, darusentan, edonentan, S-0139, sitaxsentan, TA-0201, TBC 3711, YM-598, ZD-1611 and ZD-4054. Also, salts, esters, prodrugs, metabolites, tautomers, racemates and enantiomers of the selective ET<sub>A</sub> receptor antagonists can be used for the present method when such forms are chemically feasible. For example, for enantiomeric compounds such as ambrisentan, it is intended to include their racemic forms as well as stereoisomers. Similarly, for racemic compounds such as atrasentan, it is contemplated to use its enantiomers in the present methods. Above-cited International Patent Publication No. WO 2007/119214, incorporated herein by reference in its entirety, provides a very extensive list of endothelin receptor antagonists (including individual compounds and compound classes) at pp. 7-17 thereof; any such antagonist meeting the definition of a "selective ET<sub>A</sub> receptor antagonist" herein can be used.

In one embodiment, the selective ET<sub>A</sub> receptor antagonist comprises ambrisentan ((+)-(2S)-2-[(4,6-dimethylpyrimidin-2-yl)oxy]-3-methoxy-3,3-diphenylpropanoic acid). This compound has the formula

![Chemical structure](image_url)

In another embodiment, the selective ET<sub>A</sub> receptor antagonist comprises darusentan ((+)-(S)-2-[(4,6-dimethoxypyrimidin-2-yl)oxy]-3-methoxy-3,3-diphenylpropanoic acid). This compound has the formula
In all of the above embodiments, what constitutes a "therapeutically effective amount" will depend on the particular endothelin receptor antagonist used, parameters of the individual subject, such as body weight, on the dosage form and route of administration used for the endothelin receptor antagonist, the stage or severity of the IPF, the stage or severity of PH or other complicating conditions if present, and other factors. A therapeutically effective amount in any particular situation can be readily established without undue experimentation by the physician or clinician based on the disclosure herein, for example by dosage titration with monitoring of the subject's response.

Illustratively for ambrisentan, a therapeutically effective amount will typically be found in the range of about 1 to about 25 mg/day, for example about 2 to about 15 mg/day, about 2.5 to about 10 mg/day, or about 2.5, about 3, about 3.5, about 4, about 4.5, about 5, about 6, about 7, about 8, about 9 or about 10 mg/day.

Illustratively for darusentan, a therapeutically effective amount will typically be found in the range of about 1 to about 600 mg/day, for example about 5 to about 450 mg/day, about 10 to about 300 mg/day, or about 10, about 20, about 30, about 40, about 50, about 100, about 150, about 200, about 250 or about 300 mg/day.

Higher or lower doses can be useful in specific circumstances. Useful doses of other endothelin receptor antagonists, for example selective ET\textsubscript{A} receptor antagonists, are doses that are therapeutically equivalent to the above-indicated doses of ambrisentan or darusentan.

The desired dosage amount can be administered each day, for example in individual doses administered once, twice, or three or more times a day. However, dosages stated herein on a daily or per diem basis should not be construed as necessarily requiring administration of the daily dose each and every day. For example, if the endothelin receptor
antagonist is provided in a suitably slow-release form, two or more daily dosage amounts can be administered at a lower frequency, e.g., as a depot every second day to once a month or even longer. Most typically and conveniently for the patient, the endothelin receptor antagonist is administered once a day, for example in the morning.

The endothelin receptor antagonist can be administered for an extended treatment period. Typically, the longer the treatment continues, the greater and more lasting will be the benefits. Illustratively, the treatment period can be at least about one month, for example at least about 3 months, at least about 6 months or at least about 1 year. In some cases, administration can continue for substantially the remainder of the life of the subject.

In all of the above embodiments, the endothelin receptor antagonist can be administered by any suitable route including oral, rectal, intranasal, intrapulmonary (e.g., by inhalation) or parenteral (e.g., intradermal, transdermal, subcutaneous, intramuscular or intravenous) routes. Oral administration is most convenient for the majority of subjects and can occur independently of meal times, i.e., with or without food. The endothelin receptor antagonist can be formulated together with one or more excipients in various dosage forms suitable for delivery by the above routes.

An oral dosage form useful herein typically comprises as excipients one or more pharmaceutically acceptable diluents, binding agents, disintegrants, wetting agents and/or antifrictional agents (lubricants, anti-adherents and/or glidants). Many excipients have two or more functions in a pharmaceutical composition. Characterization herein of a particular excipient as having a certain function, e.g., diluent, binding agent, disintegrant, etc., should not be read as limiting to that function. Further information on excipients can be found in standard reference works such as Handbook of Pharmaceutical Excipients, 3rd ed. (Kibbe, ed. (2000), Washington: American Pharmaceutical Association).

Suitable diluents illustratively include, either individually or in combination, lactose, including anhydrous lactose and lactose monohydrate; lactitol; maltitol; mannitol; sorbitol; xylitol; dextrose and dextrose monohydrate; fructose; sucrose and sucrose-based diluents such as compressible sugar, confectioner’s sugar and sugar spheres; maltose; inositol; hydrolyzed cereal solids; starches (e.g., corn starch, wheat starch, rice starch, potato starch, tapioca starch, etc.), starch components such as amylose and dextrates, and modified or processed starches such as pregelatinized starch; dextrins; celluloses including powdered...
cellulose, microcrystalline cellulose, silicified microcrystalline cellulose, food grade sources of α- and amorphous cellulose and powdered cellulose, and cellulose acetate; calcium salts including calcium carbonate, trisaccharide calcium phosphate, dibasic calcium phosphate dihydrate, monobasic calcium sulfate monohydrate, calcium sulfate and granular calcium lactate trihydrate; magnesium carbonate; magnesium oxide; bentonite; kaolin; sodium chloride; and the like. Such diluents, if present, typically constitute in total about 5% to about 99%, for example about 10% to about 85%, or about 20% to about 80%, by weight of the composition. The diluent or diluents selected preferably exhibit suitable flow properties and, where tablets are desired, compressibility.

[0095] Lactose, microcrystalline cellulose and starch, either individually or in combination, are particularly useful diluents.

[0096] Binding agents or adhesives are useful excipients, particularly where the composition is in the form of a tablet. Such binding agents and adhesives should impart sufficient cohesion to the blend being tableted to allow for normal processing operations such as sizing, lubrication, compression and packaging, but still allow the tablet to disintegrate and the composition to be absorbed upon ingestion. Suitable binding agents and adhesives include, either individually or in combination, acacia; tragacanth; glucose; polydextrose; starch including pregelatinized starch; gelatin; modified cellulosics including methylcellulose, carmellose sodium, hydroxypropylmethylcellulose (HPMC or hypromellose), hydroxypropylcellulose, hydroxyethylcellulose and ethylcellulose; dextrins including maltodextrin; zein; alginic acid and salts of alginic acid, for example sodium alginate; magnesium aluminum silicate; bentonite; polyethylene glycol (PEG); polyethylene oxide; guar gum; polysaccharide acids; polyvinylpyrrolidone (povidone), for example povidone K-15, K-30 and K-29/32; polyacrylic acids (carbomers); polymethacrylates; and the like. One or more binding agents and/or adhesives, if present, typically constitute in total about 0.5% to about 25%, for example about 0.75% to about 15%, or about 1% to about 10%, by weight of the composition.

[0097] Povidone is a particularly useful binding agent for tablet formulations, and, if present, typically constitutes about 0.5% to about 15%, for example about 1% to about 10%, or about 2% to about 8%, by weight of the composition.

[0098] Suitable disintegrants include, either individually or in combination, starches including pregelatinized starch and sodium starch glycolate; clays; magnesium aluminum
silicate; cellulose-based disintegrants such as powdered cellulose, microcrystalline cellulose, methylcellulose, low-substituted hydroxypropylcellulose, carmellose, carmellose calcium, carmellose sodium and croscarmellose sodium; alginates; povidone; crospovidone; polacrilin potassium; gums such as agar, guar, locust bean, karaya, pectin and tragacanth gums; colloidal silicon dioxide; and the like. One or more disintegrants, if present, typically constitute in total about 0.2% to about 30%, for example about 0.2% to about 10%, or about 0.2% to about 5%, by weight of the composition.

Croscarmellose sodium and crospovidone, either individually or in combination, are particularly useful disintegrants for tablet or capsule formulations, and, if present, typically constitute in total about 0.2% to about 10%, for example about 0.5% to about 7%, or about 1% to about 5%, by weight of the composition.

Wetting agents, if present, are normally selected to maintain the drug or drugs in close association with water, a condition that is believed to improve bioavailability of the composition. Non-limiting examples of surfactants that can be used as wetting agents include, either individually or in combination, quaternary ammonium compounds, for example benzalkonium chloride, benzethonium chloride and cetylpyridinium chloride; dioctyl sodium sulfosuccinate; polyoxyethylene alkyphenyl ethers, for example nonoxynol 9, nonoxynol 10 and octoxynol 9; poloxamers (polyoxyethylene and polyoxypropylene block copolymers); polyoxyethylene fatty acid glycerides and oils, for example polyoxyethylene (8) caprylic/capric mono- and diglycerides, polyoxyethylene (35) castor oil and polyoxyethylene (40) hydrogenated castor oil; polyoxyethylene alkyl ethers, for example ceteth-10, laureth-4, laureth-23, oleth-2, oleth-10, oleth-20, steareth-2, steareth-10, steareth-20, steareth-100 and polyoxyethylene (20) cetostearyl ether; polyoxyethylene fatty acid esters, for example polyoxyethylene (20) stearate, polyoxyethylene (40) stearate and polyoxyethylene (100) stearate; sorbitan esters; polyoxyethylene sorbitan esters, for example polysorbate 20 and polysorbate 80; propylene glycol fatty acid esters, for example propylene glycol laurate; sodium lauryl sulfate; fatty acids and salts thereof, for example oleic acid, sodium oleate and triethanolamine oleate; glyceryl fatty acid esters, for example glyceryl monooleate, glyceryl monostearate and glyceryl palmitostearate; sorbitan esters, for example sorbitan monolaurate, sorbitan monooleate, sorbitan monopalmitate and sorbitan monostearate; tyloxapol; and the like. One or more wetting agents, if present, typically constitute in total about 0.25% to about
15%, preferably about 0.4% to about 10%, and more preferably about 0.5% to about 5%, by weight of the composition.

[00101] Wetting agents that are anionic surfactants are particularly useful. Illustratively, sodium lauryl sulfate, if present, typically constitutes about 0.25% to about 7%, for example about 0.4% to about 4%, or about 0.5% to about 2%, by weight of the composition.

[00102] Lubricants reduce friction between a tableting mixture and tableting equipment during compression of tablet formulations. Suitable lubricants include, either individually or in combination, glycercyl behenate; stearic acid and salts thereof, including magnesium, calcium and sodium stearates; hydrogenated vegetable oils; glycercyl palmitostearate; talc; waxes; sodium benzoate; sodium acetate; sodium fumarate; sodium stearyl fumarate; PEGs (e.g., PEG 4000 and PEG 6000); poloxamers; polyvinyl alcohol; sodium oleate; sodium lauryl sulfate; magnesium lauryl sulfate; and the like. One or more lubricants, if present, typically constitute in total about 0.05% to about 10%, for example about 0.1% to about 8%, or about 0.2% to about 5%, by weight of the composition. Magnesium stearate is a particularly useful lubricant.

[00103] Anti-adherents reduce sticking of a tablet formulation to equipment surfaces. Suitable anti-adherents include, either individually or in combination, talc, colloidal silicon dioxide, starch, DL-leucine, sodium lauryl sulfate and metallic stearates. One or more anti-adherents, if present, typically constitute in total about 0.1% to about 10%, for example about 0.1% to about 5%, or about 0.1% to about 2%, by weight of the composition.

[00104] Glidants improve flow properties and reduce static in a tableting mixture. Suitable glidants include, either individually or in combination, colloidal silicon dioxide, starch, powdered cellulose, sodium lauryl sulfate, magnesium trisilicate and metallic stearates. One or more glidants, if present, typically constitute in total about 0.1% to about 10%, for example about 0.1% to about 5%, or about 0.1% to about 2%, by weight of the composition.

[00105] Talc and colloidal silicon dioxide, either individually or in combination, are particularly useful anti-adherents and glidants.

[00106] Other excipients such as buffering agents, stabilizers, antioxidants, antimicrobials, colorants, flavors and sweeteners are known in the pharmaceutical art and can be used in compositions of the present invention. Tablets can be uncoated or can comprise a core that is coated, for example with a nonfunctional film or a release-modifying or enteric coating. Capsules can have hard or soft shells comprising, for example, gelatin and/or HPMC,
optionally together with one or more plasticizers.

[00107] In the method of any embodiment described above, the endothelin receptor antagonist, for example selective ET<sub>A</sub> receptor antagonist, can be administered in monotherapy.

[0100] Alternatively, the endothelin receptor antagonist can be a first active agent administered in combination therapy with a second active agent effective for treatment of IPF or a condition associated therewith, for example PH. When the endothelin receptor antagonist is administered concomitantly, one of skill in the art can readily identify a suitable dose for any particular second active agent from publicly available information in printed or electronic form, for example on the internet. Illustratively and without limitation, the endothelin receptor antagonist (first active agent) can be administered with a second active agent comprising at least one drug selected from the group consisting of prostanoids, phosphodiesterase inhibitors (especially phosphodiesterase-5 (PDE5) inhibitors), endothelin receptor antagonists other than the first active agent, calcium channel blockers, diuretics, anticoagulants, oxygen and combinations thereof.

[0101] Separate dosage forms can optionally be co-packaged, for example in a single container or in a plurality of containers within a single outer package, or co-presented in separate packaging ("common presentation"). As an example of co-packaging or common presentation, a kit is contemplated comprising, in separate containers, a selective ET<sub>A</sub> receptor antagonist and at least one drug useful in combination or adjunctive therapy with the selective ET<sub>A</sub> receptor antagonist. In another example, the selective ET<sub>A</sub> receptor antagonist and the at least one drug useful in combination or adjunctive therapy with the selective ET<sub>A</sub> receptor antagonist are separately packaged and available for sale independently of one another, but are co-marketed or co-promoted for use according to the invention. The separate dosage forms can also be presented to a patient separately and independently, for use according to the invention.

[0102] The active compounds can be administered together, as described, or can be administered separately provided that administration of each compound occurs by a route, at a dosage, and within a time-frame, that permits co-action between the active compounds, through a pharmacologic or pharmacodynamic interaction, sufficient to provide beneficial outcome to a patient in need of diuresis to treat conditions such as edema.

[0103] Examples of drugs useful in combination therapy with endothelin receptor
antagonists are classified and presented in several lists below. Some drugs are active at more than one target; accordingly certain drugs may appear in more than one list. Use of any listed drug in a combination is contemplated herein, independently of its mode of action. Endothelin receptor antagonists, other than the first active agent, useful as the second active agent in combination therapies herein can be selected from those mentioned hereinabove, including dual or non-selective ET_A/ET_B receptor antagonists such as bosentan.

[0104] A suitable prostanoid can be illustratively selected from beraprost, cicaprost, epoprostenol, iloprost, NS-304, PGEi, prostacyclin, treprostinil and combinations thereof.

[0105] A suitable PDE5 inhibitor can illustratively be selected from sildenafil, tadalafil, vardenafil and combinations thereof.

[0106] A suitable calcium channel blocker can illustratively be selected from the following list:

Aryklalkylamines: bepridil, clentiazem, diltiazem, fendiline, gallopamil, mibebradil, prenylamine, semotiadil, terodiline, and verapamil

Dihydropyridine derivatives: amlodipine, aranidipine, barnidipine, benidipine, cilnidipine, efonidipine, elgodipine, felodipine, isradipine, lacidipine, lercanidipine, manidipine, nicardipine, nifedipine, nilvadipine, nimodipine, nisoldipine, nitrendipine, and NZ 105

Piperazine derivatives: cinnarizine, dotarizine, flunarizine, lidoflazine, and lomerizine

Unclassified: bencyclane, etafenone, fantofarone, monatepil, and perhexiline

Particularly suitable calcium channel blockers include amlodipine, diltiazem, felodipine, isradipine, nicardipine, nifedipine, nisoldipine, verapamil and combinations thereof.

[0107] In an embodiment, a present method comprises administration of a selective ET_A receptor antagonist in combination with at least one diuretic, wherein the selective ET_A receptor antagonist is ambrisentan or darusentan. A diuretic is known to be useful to treat various conditions such as heart failure, liver cirrhosis, hypertension and certain kidney diseases. In a particular embodiment, the diuretic is administered with a selective ET_A receptor antagonist concomitantly or separately to a patient to treat edema. It is observed that there is a causal association between selective ET_A receptor antagonist (such as ambrisentan and darusentan) and fluid retention and that there is a greater incidence and severity of
peripheral edema in elderly patients. Thus, effective fluid management by co-administration of at least one diuretic can be beneficial to patients taking such selective ET\textsubscript{A} receptor antagonists.

[0108] A suitable diuretic can illustratively be selected from the following list:

5 **Organomercurials:** chlormerodrin, chlorothiazide, chlorthalidone, meralluride, mercaptomerin sodium, mercumatilin sodium, mercurous chloride, and mersalyl

**Purines:** pamabrom, protheobromine, and theobromine

**Steroids:** canrenone, oleanandr, spironolactone (ALDACTONE\textsuperscript{®}), and eplerenone (INSPRA\textsuperscript{®})

10 **Sulfonamide derivatives:** acetazolamide, ambuside, azosemide, bumetanide, butazolamide, chloraminophenamide, clofenamide, clogamid, clorexlone, disulfamid, ethoxolamide, furosemide, mefruside, methazolamide, piretanide, torsemide, tripamide, and xipamide

**Thiazides and analogs:** althiazide, bendroflumethiazide, benzthiazide, benzylhydrochlorothiazide, buthiazide, chlorthalidone, cyclopenthiazide, cyclothiazide, ethiazide, fenquizone, hydrochlorothiazide, hydroflumethiazide, indapamide, methyclothiazide, metolazone, paraflutizide, polythiazide, quinethazone, teclothiazide, and trichlormethiazide

**Uracils:** aminomometradsine

**Unclassified:** amiloride, Biogen BG 9719, chlorazanil, ethacrynic acid, etozen, isosorbide,

20 Kiowa Hakko KW 3902, mannitol, muzolimine, perhexine, Sanofi-Aventis SR 121463, ticrynafen, triamterene, and urea

Particularly suitable diuretics include spironolactone and eplerenone because they are renal competitive aldosterone antagonists in a class of pharmaceuticals called potassium-sparing diuretics.

[0109] In some embodiments, the diuretic if present comprises a thiazide or loop diuretic. Thiazide diuretics are generally not preferred where the patient has a complicating condition such as diabetes or chronic kidney disease, and in such situations a loop diuretic can be a better choice.

[0110] Particularly suitable thiazide diuretics include chlorothiazide, chlorthalidone,
hydrochlorothiazide, indapamide, metolazone, polythiazide and combinations thereof. Particularly suitable loop diuretics include bumetanide, furosemide, torsemide and combinations thereof.

[0111] A suitable anticoagulant can illustratively be selected from acenocoumarol, ancred, anisindione, bromindione, clorindione, coumetarol, cyclocumarol, dextran sulfate sodium, dicumarol, diphenadione, ethyl biscoumacetate, ethylidene dicoumarol, fluindione, heparin, hirudin, lyapolate sodium, pentosan polysulfate, phenindione, phenprocoumon, phosvitin, picotamide, tioclomarol, warfarin and combinations thereof.

[0112] When the endothelin receptor antagonist is used in combination therapy with at least one second active agent, the endothelin receptor antagonist and the at least one second active agent can be administered at different times or at about the same time (at exactly the same time or directly one after the other in any order). The endothelin receptor antagonist and the at least one second active agent can be formulated in one dosage form as a fixed-dose combination for administration at the same time, or in two or more separate dosage forms for administration at the same or different times.

[0113] Separate dosage forms can optionally be co-packaged, for example in a single container or in a plurality of containers within a single outer package, or co-presented in separate packaging ("common presentation"). As an example of co-packaging or common presentation, a kit is contemplated comprising, in separate containers, the endothelin receptor antagonist and at least one drug useful in combination therewith as disclosed herein. In another example, the endothelin receptor antagonist and the at least one drug useful in combination therapy therewith are separately packaged and available for sale independently of one another, but are co-marketed or co-promoted for use according to the present invention. The separate dosage forms can also be presented to a patient separately and independently, for use according to the present invention.

[0114] In one embodiment at least the endothelin receptor antagonist (e.g., ambrisentan) is provided in an orally deliverable formulation. The endothelin receptor antagonist (e.g., ambrisentan) formulation can be adapted for any suitable frequency of administration, but in one embodiment is adapted for once a day oral administration.

[0115] In one embodiment the second active agent is provided in an orally deliverable formulation; for example a formulation adapted for once a day oral administration. The
second active agent is typically present in the combination in an amount providing an adequate to full dose of that agent.

[0116] Mention of a particular drug or second active agent in the present specification and claims will be understood, except where the context demands otherwise, to include pharmaceutically acceptable salts, esters, prodrugs, metabolites, racemates and enantiomers of the drug, to the extent that such salts, esters, prodrugs, metabolites, racemates or enantiomers exist and are therapeutically effective.

EXAMPLES

[0117] The following examples are merely illustrative, and do not limit this disclosure in any way. Reference is made to "primary" and "secondary" endpoints or objectives of a clinical trial. These endpoints or objectives should not necessarily be considered "primary" or "secondary" with respect to the present invention.

[0118] Abbreviations used in the present examples are explained in Table 1.

Table 1. List of abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>6MWD</td>
<td>six-minute walk distance</td>
</tr>
<tr>
<td>6MWT</td>
<td>six-minute walk test</td>
</tr>
<tr>
<td>ALT</td>
<td>alanine aminotransferase</td>
</tr>
<tr>
<td>AST</td>
<td>Aspartate aminotransferase</td>
</tr>
<tr>
<td>ATS</td>
<td>American Thoracic Society</td>
</tr>
<tr>
<td>BDI</td>
<td>Borg dyspnea index</td>
</tr>
<tr>
<td>DLCO</td>
<td>Diffusing capacity of the lung for carbon monoxide</td>
</tr>
<tr>
<td>ECG</td>
<td>electrocardiogram</td>
</tr>
<tr>
<td>EQ5D</td>
<td>Euro-QoL (5 domains)</td>
</tr>
<tr>
<td>ERS</td>
<td>European Respiratory Society</td>
</tr>
<tr>
<td>FEV₁</td>
<td>forced expiratory volume in 1 second</td>
</tr>
<tr>
<td>FEV₁ (L)</td>
<td>forced expiratory volume in 1 second, expressed in liters</td>
</tr>
<tr>
<td>FVC</td>
<td>forced vital capacity</td>
</tr>
<tr>
<td>FVC (L)</td>
<td>forced vital capacity, expressed in liters</td>
</tr>
<tr>
<td>GGT</td>
<td>gamma-glutamyl aminotransferase</td>
</tr>
<tr>
<td>HRCT</td>
<td>high-resolution computerized tomography</td>
</tr>
<tr>
<td>ICF</td>
<td>informed consent form</td>
</tr>
<tr>
<td>ILD</td>
<td>interstitial lung disease</td>
</tr>
<tr>
<td>IMP</td>
<td>investigative medicinal product</td>
</tr>
<tr>
<td>IPF</td>
<td>idiopathic pulmonary fibrosis</td>
</tr>
<tr>
<td>LAS</td>
<td>lung allocation score</td>
</tr>
<tr>
<td>LFT</td>
<td>liver function test</td>
</tr>
<tr>
<td>LLN</td>
<td>lower limit of normal</td>
</tr>
</tbody>
</table>
A Phase 3, randomized, double-blind, placebo-controlled, multi-center, parallel-group, event-driven study is conducted to evaluate the efficacy and safety of ambrisentan in subjects with early IPF.

The primary objective of the study is to determine if ambrisentan is effective in delaying disease progression and death in subjects with IPF.

Secondary objectives include evaluation of the safety and effect of ambrisentan on development of PH, quality of life and dyspnea symptoms in this patient population.

Exploratory evaluations include changes in other disease-related assessments and biomarkers related to IPF pathogenesis. Blood is collected and stored for later analysis to determine relationships between serum and plasma marker levels and relation to treatment effect and measures of outcomes.

The primary endpoint is time to death or disease progression; defined as the first occurrence of any of the following:

1. a decrease of >10% in FVC (L);
2. respiratory hospitalization;
3. all-cause mortality.

Deterioration in FVC is confirmed at a subsequent study visit within 28 (± 14)
days. Respiratory hospitalization is adjudicated by a blinded endpoint committee.

Secondary endpoints include:

- proportion of subjects with disease progression or death at Visit 7 (48 weeks);
- change in pulmonary function (FVC and DLCO) tests at Visit 7;
- change in 6MWD at Visit 7;
- change in QoL score at Visit 7 as assessed by:
  - SF-36;
  - SGRQ;
- change in dyspnea score at Visit 7 as assessed by TDI;
- among subjects without PH at baseline, the proportion who develop PH on-study (documented by RHC).

Other endpoints of interest include:

- change in UNOS LAS at Visit 7;
- changes from baseline in pulmonary function tests, 6MWD, QoL scores and dyspnea scores (TDI) at clinic visits other than Visit 7;
- biomarker assessments to evaluate any potential relationship with prognosis or disease outcome after treatment;
- change in hemodynamic parameters at Visit 7 as assessed by RHC;
- changes in QoL as assessed by EQ5D;
- changes in radiographic findings related to IPF on pulmonary HRCT.

This study consists of three periods: screening period (28 days), titration period (14 days) and treatment period (up to 1092 days).

At the end of the screening period (Visit 2, randomization), subjects are randomized and receive their first dose of IMP (5 mg ambrisentan or placebo); subjects receive this dose of IMP once daily for the duration of the 14-day titration period. At the end of the titration period (Visit 3) the ambrisentan dose is up-titrated to 10 mg.

During the treatment period subjects receive 10 mg ambrisentan or placebo from the beginning of the treatment period through the remainder of the study.

A total of 2 blinded dose reductions (i.e., 10 mg to 5 mg) are permitted during the
treatment period if the investigator deems necessary for subject safety. Once a dose reduction is performed during the treatment period, a titration back up to 10 mg is performed for that subject, similar to the initial 14-day titration period. If the investigator again deems a dose reduction is necessary for subject safety or tolerability, the subject may have a second and final dose reduction from 10 mg to 5 mg. After a second dose reduction, the subject then remains at 5 mg daily. Dose reductions are not considered if it has been fewer than 28 days since a titration has been completed.

[0131] Visits occur every 84 ± 6 days during the treatment period.
[0132] A total target number of 600 subjects with IPF are randomized in a 2:1 ratio to either ambrisentan (400 subjects) or placebo (200 subjects).
[0133] Subjects must meet all of the following inclusion criteria for participation in this study.

1. Male or females from 40 to 80 years of age.
2. Diagnosis of IPF based on ATS-ERS guidelines within 3 years prior to study enrollment. Within 90 days of study enrollment, diagnosis must be confirmed by HRCT.
3. Honeycombing <5% as assessed on HRCT; if necessary, HRCT results undergo a core review process to confirm diagnosis.
4. Willingness to undergo RHC at baseline and at Visit 7 or end of study.
5. Willingness and ability to comply with required monitoring of liver function every 28 days. LFTs include serum ALT, AST, alkaline phosphatase, GGT and total bilirubin concentrations.
6. FVC >50 to <90% of predicted with a ratio of FEVi (L) / FVC (L) >0.65. PFTs must be completed no more than 90 days before enrollment.
7. Ability to perform and complete 6MWT at screening.
8. Negative serum pregnancy test at screening and negative urine pregnancy test at randomization for female subjects of childbearing potential.
9. Female subjects of childbearing potential must be willing to use at least two reliable methods of contraception throughout their participation in the study and 30 days after discontinuation of IMP unless the subject has had a tubal sterilization, is postmenopausal, or has a Copper T 380A or LNg 20 intrauterine device inserted,
in which case no other contraception is needed. Subjects of child bearing potential must also be willing to undergo pregnancy tests every 28 days.

10. Male subjects must be capable of understanding and acknowledging potential risks of testicular tubular atrophy and infertility associated with taking this IMP as described in the ICF.

11. Competency to understand the information given in the ICF. Subjects must sign the ICF prior to initiation of any study procedures, unless the assessment is performed as standard of care for this disease.

[0134] Subjects who meet any of the following exclusion criteria are not enrolled in this study.

1. Diagnosis of an ILD or restrictive lung disease other than UIP or IPF.
2. Obstructive lung disease as determined by evidence of airflow obstruction on HRCT or physiological criteria including:
   a. FEV1 / FVC ratio <0.65;
   b. RV >120% by plethysmography or significant (verified by radiologist) emphysema on HRCT if plethysmography not available;
   c. evidence of reactive airway disease by change in FEV1 of >15% following bronchodilator challenge.
3. Evidence of sustained improvement of IPF condition defined as improvement from pre-therapy PFTs observed with two or more successive post-therapy PFTs over the year prior to randomization.
4. Condition(s) that is/are a contraindication for RHC including:
   o tricuspid or pulmonary valve stenosis;
   o prosthetic tricuspid or pulmonary valve;
   o right atrial or right ventricular masses;
   o cyanotic heart disease;
   o allergy to latex or catheter material;
   o previous pneumonectomy.
5. Active or recent (<56 days prior to enrollment) pulmonary or upper respiratory tract infection.
6. Hospitalization within 56 days of screening for an acute exacerbation of IPF.
7. Chronic heart failure (NYHA class III/IV) or known left ventricular ejection fraction <25%.
8. Acute or chronic impairment (other than dyspnea) which limits the ability to comply with study requirements and procedures including the 6MWT.
9. Treatment with ambrisentan in a clinical study or with commercial product.
10. Treatment with an approved or experimental endothelin receptor antagonist within 28 days prior to randomization.
11. Chronic use of sildenafil or other PDE-5 inhibitor for PH.
12. Chronic treatment with immunosuppressive, cytotoxic or antifibrotic drugs including pirfenidone, D-penicillamine, colchicine, TNF-α antagonists, imatinib, interferon-gamma, cyclophosphamide, cyclosporine A or azathioprine within 28 days of randomization.
13. Prior endothelin receptor antagonist treatment discontinued for reasons other than those associated with liver function abnormalities (including documented drug interactions and hypersensitivity).
14. ALT or AST >1.5 x ULN at screening.
15. Hemoglobin concentration <75% of LLN at screening.
16. Serum creatinine >2.5 mg/dl (221 µmol/l) or subject requires hemodialysis, peritoneal dialysis or hemofiltration.
17. Systolic blood pressure <85 mmHg.
18. History of malignancies within the past 5 years, with the exception of basal cell carcinoma of the skin or successfully treated in situ carcinoma of the cervix.
19. Female who is pregnant or nursing.
20. Known history of alcohol abuse within 1 year of enrollment.
21. Participation in a clinical study involving another investigational drug or device within 28 days of screening.
22. Comorbid condition or illness limiting life expectancy to <1 year at time of screening.
23. Serious or active medical or psychiatric condition which, in the opinion of the investigator, would interfere with subject treatment, assessment or compliance with the protocol.
Only persons not involved in the day-to-day conduct of the study know the randomization code before unblinding. Randomization is performed with use of an interactive voice response system. Prior to randomization, eligible subjects are stratified by baseline presence of PH and whether SLB has been performed to confirm diagnosis. Within the four strata (baseline PH [yes/no] and SLB [yes/no]), subjects are randomized in a 2:1 ratio to receive ambrisentan or placebo.

Blinding is accomplished by providing IMP (ambrisentan or placebo) in tablets that are visually indistinguishable and provided in numbered containers. Only the numbers of the containers administered to a given study subject, and not the identity of the IMP, are provided to sites.

IMP is provided in the form of pink, plain-faced, film-coated, immediate-release tablets, containing either zero mg (placebo), 5 mg, or 10 mg ambrisentan. Ambrisentan tablets contain lactose monohydrate, microcrystalline cellulose, croscarmellose sodium and magnesium stearate and are film-coated with hypromellose, red iron oxide, talc, polyethylene glycol and titanium dioxide.

Placebo tablets contain lactose monohydrate, microcrystalline cellulose, croscarmellose sodium and magnesium stearate and are film-coated with hypromellose, red iron oxide, talc, polyethylene glycol and titanium dioxide.

IMP (ambrisentan or placebo) is taken orally, with or without food, every day in the morning throughout the course of the study unless instructed otherwise.

Subjects are instructed to record whether or not they have taken their daily dose of IMP in the study diary. Subjects are instructed to bring their study diary, as well as the used and unused IMP containers with them to every visit to assess compliance and drug accountability. IMP compliance is assessed via a telephone call 2 days prior to the day of a safety visit.

All study visit dates are determined from the date of first dose of IMP, and all study visit windows are ± 6 days, except for the randomization (Visit 2) evaluations which occur on the day of the first dose (Day 0).

All subjects have blood drawn every 28 ± 2 days (from Day 0) for LFTs. LFTs include serum ALT, AST, alkaline phosphatase, GGT, and total bilirubin concentrations. The results of these tests are reviewed by the investigator immediately upon receipt. An increase in serum ALT or AST concentration >3 x ULN is confirmed by a second test that is collected
no more than 7 days after receipt of the initial lab report. Confirmed serum ALT or AST concentration >3 x ULN is immediately reported as a serious adverse event. Patients with ALT or AST concentrations >3 x ULN have LFTs performed every 14 ± 2 days until the results are <3 x ULN.

[0143] Diagnosis of IPF by HRCT demonstrates a symmetrical pattern of bibasilar, peripheral and subpleural intralobular septal thickening, fibrotic changes, honeycombing and traction bronchiectasis and bronchiolectasis. There may be associated ground glass opacity of the lungs. Findings on HRCT are confirmed first at the site by a radiologist. If the findings are not confirmed or are inconclusive, a central core review confirms the features including presence of <5% honeycombing, and for clinically significant features of obstructive disease that are exclusionary. As an exploratory assessment at participating sites only, follow-up pulmonary HRCT is performed at Visit 7 or end of study to evaluate changes in radiographic findings related to IPF (e.g., ground glass changes) that is scored or graded. Prone pulmonary HRCT films are performed in these subjects and the films reviewed and scored for changes.

HRCT is performed and recorded according to a central imaging vendor and instruction is provided by the vendor in a technical manual. Technique includes slices with a thickness of 1-1.5 mm that have been reconstructed with an algorithm that maximizes spatial resolution. Images include supine, prone and expiratory images.

[0144] The following procedures are completed at the RHC Visit. RHC is performed once during screening period and at end of study or early termination visit (+ 3 days) if the subject consents and at the discretion of the investigator; or RHC is performed at Visit 7 in all subjects who had not completed an end of study or early termination visit prior to that time point. Hemodynamic parameters are measured at the time of the RHC procedures, including mPAP, RAP, PVR, PCWP and cardiac output. If severe PH is detected with the RHC during screening, and entry criteria are otherwise met, exclusion of the subject is at the investigator's discretion.

[0145] Spirometry is performed according to ATS standards at all visits. Subjects perform as least three spirometry maneuvers that achieve ATS standards. The best FVC is recorded. DLCO is corrected for serum hemoglobin concentration and is measured along with FVC as a part of the secondary endpoint assessments. PFT measures for screening also require residual volume determination and assessment for bronchial airway reactivity as needed (i.e., bronchodilator challenge testing).
[0146] A 12-lead ECG is performed at the screening and end of study visits. A copy of each ECG is maintained at the site. Any clinically relevant ECG findings are captured. Any clinically relevant change since the screening visit is captured as an adverse event.

[0147] The 6MWT test is conducted according to ATS guidelines in accordance with local standard operating procedures. The 6MWT is performed at all visits except Visit 3. Pulse oximetry is performed and recorded on case report forms during the 6MWT to determine if post-exercise hypoxia or oxygen desaturation occurs.

[0148] Disease progression of IPF is defined as any of the following occurring in a subject: a decrease of >10% in FVC (L) confirmed in 28 ± 14 days, respiratory hospitalization, and death (all-cause mortality). When disease progression occurs it may be related to an acute exacerbation of IPF, which may also require hospitalization for treatment of the exacerbation. Acute exacerbation of IPF has been defined as:

- unexplained worsening or development of dyspnea within a 30 day period;
- HRCT with new bilateral ground-glass abnormality and/or consolidation superimposed on a background of reticular or honeycomb pattern consistent with UIP pattern;
- no evidence of pulmonary infection, by endotracheal aspirate or bronchoalveolar lavage if available;
- exclusion of alternative causes, including
  - left heart failure;
  - pulmonary embolism;
  - identifiable cause of acute lung injury

[0149] Chemistry and hematology are collected at every visit and at early termination (if applicable). A central laboratory analyzes all protocol-specified clinical laboratory tests at clinic visits; collection, processing, labeling and shipping of the samples is completed following central laboratory guidelines. Local laboratories analyze all protocol-specified laboratory tests at 28-day intervals between clinic visits and if serum aminotransferase elevations >3 x ULN occur there is a second test to confirm whether elevations are >3 x ULN. Additional laboratory tests may be performed by a local laboratory or the central laboratory (unscheduled visit) if clinically relevant abnormal values are obtained at any time.
during the course of the study.

The following chemistry tests are required at each clinic study visit: serum ALT, AST, alkaline phosphatase, GGT, total bilirubin, creatinine, amylase, blood urea nitrogen, sodium, potassium, chloride, bicarbonate, calcium, uric acid, glucose, total protein and albumin.

The following hematology tests are required at each clinic study visit: hemoglobin, hematocrit, red cell count, red cell indices, white blood cell count (total and differential) and platelet count.

Coagulation: prothrombin time is performed at Visit 1 (screening) and end of study.

The following tests are required at each 28-day interval:

- LFTs: serum ALT, AST, alkaline phosphatase, GGT, total bilirubin, creatinine.
- Serum pregnancy tests are performed for all female subjects of child-bearing potential at the screening visit, for each study visit following Day 0, including LFT laboratory visits and early termination, if applicable. In addition, one urine pregnancy test is performed at Visit 2 (prior to randomization).
- Biomarkers: Blood is collected, at selected sites only, at baseline (Day 0) and Visits 5 and 7 or end of study and stored to measure levels of proteins in the serum and/or plasma to determine if and how they fluctuate and correlate with disease activity, treatment effect and predict outcomes in subjects. These markers include KL-6, surfactant proteins SP-A and SP-D, BNP and NT-pro-BNP, as well as CCL-2 and CCL-18 and ET-1/ET-3 ratio. Biomarkers are performed when the on-study RHC is performed at Visit 7 or when a RHC is performed at an end of study or early termination visit prior to Visit 7.

Questionnaires for the TDI, SGRQ, EQ5D and SF-36 are completed by study personnel with the subject. These assessments are performed prior to any other procedures. Following Visit 7, these procedures are performed at every other visit.

**Example 2**

A Phase 3, randomized, double-blind, placebo-controlled, multi-center, parallel-group study is conducted to evaluate ambrisentan therapy in subjects with PH and IPF.

The primary objective of this study is to compare the change in 6MWD after
initiating ambrisentan or placebo treatment in subjects with PH and IPF.

The secondary objectives of this study are to evaluate changes in other clinical measures of PH and IPF after initiating ambrisentan or placebo treatment, including long-term survival, dyspnea symptoms, WHO functional class, PFTs, quality of life, and serum NT-proBNP concentrations.

Safety and tolerability of ambrisentan treatment are compared to placebo treatment.

A target number of 220 subjects are randomized 2:1 to ambrisentan 10 mg (147 subjects) or placebo (73 subjects). The target population comprises men and women of 40 to 75 years of age with PH diagnosed by RHC and IPF diagnosed in accordance with ATS-ERS guidelines within 3 years prior to study enrollment.

The study period includes 48 weeks of blinded, placebo-controlled treatment followed by 12 weeks of blinded ambrisentan treatment.

For enrollment, subjects must have

1. a confirmed diagnosis of PH, defined by the following hemodynamic criteria and documented by means of RHC performed within 1 year prior to screening:
   a. mPAP > 25 mmHg;
   b. PVR > 240 dyne.sec/cm\(^5\); and
   c. PCWP or LVEDP < 15 mmHg; or
2. documented clinical evidence to suggest presence of PH based upon one or more of the following findings:
   a. right ventricular systolic pressure > 45 mmHg estimated by echocardiography;
   b. radiographic evidence of right ventricular enlargement;
   c. serum B-type natriuretic peptide concentrations > 100 pg/ml;
   d. DLCO < 40% of predicted concurrent with a requirement for supplemental oxygen.

Additional eligibility criteria are as follows.

1. Subject who does not have a confirmed diagnosis of PH documented by historical RHC data and is suspected of having PH must agree to undergo a RHC as part of the screening process to confirm the diagnosis of PH.
2. Subject must have a diagnosis of IPF made in accordance with ATS-ERS
guidelines within 3 years prior to study enrollment.
3. Subject must have FVC > 30% of predicted.
4. Subject, with or without supplemental oxygen, must have a resting arterial oxygen saturation (SaO₂) ≥ 90% as measured by pulse oximetry at the screening visit.
5. Subject must be able to walk a distance of at least 25 m during the screening 6MWT to be eligible for randomization.
6. Subject must meet the following hematology criteria at the screening visit:
   a. hemoglobin concentration > 10 g/dl;
   b. hematocrit ≥ 30%.
7. Subject receiving calcium channel blockers or HMG-CoA reductase inhibitors must be on stable therapy for at least 4 weeks prior to the screening visit.
8. Subject must agree not to enroll in an exercise training program for pulmonary rehabilitation during the first 12 weeks of the study.
9. Female subject of childbearing potential must have a negative serum pregnancy test at the screening visit and a negative urine pregnancy test at the randomization visit.
10. Female subject of childbearing potential must agree to use two reliable methods of contraception from the screening visit until study completion and for at least 30 days following the last dose of study drug.
11. Male subject must be informed of the potential risks of testicular tubular atrophy and infertility associated with taking this study drug and queried regarding his understanding of the potential risks.
12. Subject must agree not to participate in a clinical study involving another investigational drug or device throughout this study.
13. Subject must be competent to understand the information given in the ICF and must sign the form prior to the initiation of any study procedure.

This Phase 3 randomized, double-blind, placebo-controlled, multicenter study compares safety and efficacy of ambrisentan 10 mg daily to placebo in subjects with IPF and PH. This study consists of three periods: a screening period, a 48-week placebo-controlled treatment period, and a 12-week ambrisentan treatment period.

Eligible subjects who do not have historical documentation of PH by RHC are required to undergo RHC as part of the screening process to confirm the diagnosis of PH.
[0165] Eligible subjects are stratified based on the magnitude of their pulmonary hypertension (mPAP > 25 but ≤ 30 mmHg and mPAP > 30 mmHg) at screening, and are randomized 2:1 to ambrisentan or placebo. Subjects randomized to ambrisentan treatment receive 5 mg ambrisentan once daily for 4 weeks and 10 mg ambrisentan once daily for 44 weeks. Subjects randomized to placebo receive a placebo tablet (identical in appearance to ambrisentan) once daily for 48 weeks. After the Week 4 visit, a blinded dose reduction of study drug is permitted if a subject is not tolerating study drug (i.e., 10 mg to 5 mg; 5 mg to 5 mg, or placebo to placebo). A maximum of 1 request for a dose reduction is permitted for each treatment period. Following a down-titration, a blinded rechallenge (i.e., an up-titration) may be requested per investigator discretion.

[0166] After 48 weeks of blinded treatment with study drug, all subjects receive ambrisentan treatment, blinded to dose, for an additional 12 weeks. Subjects initially randomized to ambrisentan continue receiving their current dose. Subjects initially randomized to placebo will receive 5 mg once daily for 4 weeks before up-titrating to 10 mg once daily for 8 weeks. Subject treatment assignments remain blinded for the duration of the study. At completion of this study, subjects may be eligible for additional ambrisentan treatment in a long-term, open-label study.

[0167] Subjects are monitored with clinical laboratory tests monthly throughout the study. Subjects are also assessed for safety and efficacy at screening, randomization (Week 0), and at Weeks 4, 8, 12, 24, 36, 48, 52 and 60.

[0168] At clinic visits, 6MWD, BDI and PFTs are assessed at trough study drug plasma concentrations. Study drug plasma concentrations are considered at trough if administration was at least 16 hours prior to the assessment(s). Therefore, on the day of a study visit, subjects hold their study drug until 6MWD, BDI and PFTs have been assessed.

[0169] The 6MWT is administered on the subject's "usual" oxygen. If the subject normally requires supplemental oxygen with ambulation, (s)he performs the test with supplemental oxygen. Subjects who require supplemental oxygen receive the same oxygen flow rate they were receiving at the randomization visit during all subsequent 6MWTs. If the oxygen flow rate must be increased during subsequent visits due to safety concerns, the 6MWT should be conducted at the increased oxygen flow rate. If the subject reduces or discontinues supplemental oxygen use during the study, (s)he should still perform the 6MWT
with the same flow rate of oxygen that was used during previous tests.

[0170] Drug and placebo are provided as oral tablets.

[0171] The primary efficacy endpoint is change from baseline in 6MWD evaluated after 12 weeks.

5 [0172] Secondary endpoints include:

- long-term survival, as defined by the time from randomization to first occurrence of death (all-cause);
- change from baseline measured at 12 weeks in:
  - BDI immediately following exercise;
  - WHO functional class;
  - PFTs: FVC, % predicted; DLCO, % predicted;
  - CAMPHOR QoL assessment;
  - serum NT-proBNP.

[0173] Exploratory endpoints include:

15 - change in 6MWD, BDI, WHO functional class, PFTs, QoL measures and NT-proBNP over time;
- change in oxygen saturation parameters over time:
  - supplemental oxygen requirement (defined as resting \( \text{SpO}_2 < 88\% \));
  - desaturation to < 88% at the end of the 6MWT.

20 [0174] Prior to randomization, eligible subjects are stratified based on the magnitude of their pulmonary hypertension (mPAP > 25 but ≤ 30 mmHg and mPAP > 30 mmHg) at screening. Within the two strata, subjects are randomized 2:1 to receive ambrisentan or placebo. The full analysis set includes all subjects randomized to treatment who receive at least one dose of study drug, analyzed according to randomized treatment group. This is the primary analysis set for assessing efficacy. The safety analysis set also includes all subjects randomized to treatment who receive at least one dose of study drug, but safety data are summarized according to treatment actually received.

[0175] Analysis of the primary efficacy endpoint, the change from baseline in 6MWD measured after 12 weeks, compares ambrisentan treatment to placebo treatment. A 2-sided stratified Wilcoxon rank sum test at \( \alpha = 0.05 \) is used. The mean and 95% confidence intervals
from normal theory provide the primary estimate of treatment effect. In addition, the Hodges-Lehmann estimate of treatment effect and associated 95% confidence interval are reported. Based on a 2-sided, 2-sample t-test (α = 0.05) and a standard deviation of 75 meters (m), a total of 220 subjects (147 randomized to ambrisentan, and 73 subjects randomized to placebo) has approximately 90% power to detect an average placebo-adjusted change from baseline in 6MWD at Week 12 of 35 m.

[0176] Analyses of the secondary efficacy endpoints compare ambrisentan treatment to placebo treatment. The endpoints of BDI, WHO functional class, PFTs (FVC, DLCO), CAMPHOR QoL and log-transformed NT-proBNP are tested using the same method as described for the primary endpoint.

[0177] Survival, defined as time from randomization to first occurrence of death (all-cause), is displayed as a Kaplan-Meier event-free curve for each treatment group. Differences between the curves are tested using the log-rank statistic. The hazard ratio is used to characterize treatment effect and 95% confidence intervals are calculated using a Cox proportional hazards regression model.

[0178] A fixed sequence approach is used to control the type 1 error rate for the three most important secondary endpoints, namely survival, change in BDI, and change in WHO functional class. If the primary efficacy analysis of change in 6MWD demonstrates statistical significance (p ≤ 0.05), then survival at 48 weeks will be tested at α = 0.05. If survival at Week 48 demonstrates statistical significance, then the change in BDI at Week 12 is tested at α = 0.05. If the change in BDI at Week 12 demonstrates statistical significance, then the change in WHO functional class is tested at α = 0.05.

[0179] All patents and publications cited herein are incorporated by reference into this application in their entirety.

[0180] The words "comprise", "comprises", and "comprising" are to be interpreted inclusively rather than exclusively.
WHAT IS CLAIMED IS:

1. A method for inhibiting development of pulmonary hypertension (PH) in a subject having idiopathic pulmonary fibrosis (IPF), the method comprising administering a therapeutically effective amount of a selective ET<sub>A</sub> receptor antagonist to the subject, wherein the subject at baseline does not have a diagnosis of PH.

2. The method of Claim 1, that following onset of PH in the subject is effective to retard or arrest progression of the PH.

3. The method of Claim 1, that is further effective to provide a reduction of at least about 25% in probability of a clinical worsening event during treatment, by comparison with placebo.

4. The method of Claim 1, that is further effective to improve or inhibit decline in the subject's exercise capacity.

5. The method of Claim 1, that is further effective to inhibit worsening of or to ameliorate quality of life and/or dyspnea in the subject.

6. The method of Claim 1, wherein the subject at baseline has zero to about 5% honeycombing.

7. The method of Claim 1, wherein the subject at baseline has greater than about 3.3% honeycombing.

8. The method of Claim 1, wherein the subject at baseline has a clinical diagnosis of IPF, the diagnosis having been made without surgical lung biopsy.

9. The method of Claim 8, wherein the diagnosis has been made with the aid of HRCT.

10. The method of Claim 1, wherein the selective ET<sub>A</sub> receptor antagonist is administered orally once a day.

11. The method of Claim 1, wherein the selective ET<sub>A</sub> receptor antagonist is administered by inhalation.

12. The method of Claim 1, wherein the selective ET<sub>A</sub> receptor antagonist has an ET<sub>A</sub>/ET<sub>B</sub> selectivity ratio of at least about 500 by the Greene method.
13. The method of Claim 1, wherein the selective ET<sub>A</sub> receptor antagonist comprises at least one agent selected from the group consisting of ambrisentan, atrasentan, avosentan, BMS 193884, BQ-123, CI-1020, clazosentan, darusentan, edonentan, S-0139, sitaxsentan, TA-0201, TBC 3711, YM-598, ZD-1611, and ZD-4054.

14. The method of Claim 1, wherein the selective ET<sub>A</sub> receptor antagonist comprises ambrisentan.

15. The method of Claim 14, wherein the ambrisentan is administered in a daily dosage amount of about 1 mg to about 25 mg.

16. The method of Claim 1, wherein the subject at baseline has a clinical diagnosis of IPF, the diagnosis having been made without surgical lung biopsy and wherein the method comprises administering about 1 mg to about 25 mg ambrisentan.

17. The method of Claim 1, wherein the selective ET<sub>A</sub> receptor antagonist comprises darusentan.

18. The method of Claim 17, wherein the darusentan is administered in a daily dosage amount of about 1 mg to about 600 mg.

19. The method of Claim 1, wherein the subject at baseline has a clinical diagnosis of IPF, the diagnosis having been made without surgical lung biopsy and wherein the method comprises administering about 1 mg to about 600 mg darusentan.

20. The method of Claim 1, wherein the selective ET<sub>A</sub> receptor antagonist is administered as a first agent in combination therapy with a second agent which is effective for treatment of IPF, PH or a condition associated IPF or PH.

21. The method of Claim 1, the selective ET<sub>A</sub> receptor antagonist is administered as a first agent in combination therapy with a second agent which is effective for treatment of edema.

22. The method of Claim 21, wherein the second agent comprises at least one diuretic selected from the group consisting of chloromerodrin, chlorothiazide, chlorthalidone, mercalluride, mercaptomerin sodium, mercumatilin sodium, mercurous chloride, mersalyl, pamabrom, protheobromine, theobromine<sub>α</sub>, canrenone, oleandrin,
spironolactone, eplerenone, acetazolamide, ambuside, azosemide, bumetanide, butazolamide, chloraminophenamide, clofamidine, clopamide, clorexolone, disulfamide, ethoxzolamide, furosemide, mefruside, methazolamide, piretanide, torsemide, tripamide, xipamide, althiazide, bendroflumethiazide, benzthiazide, benzylhydrochlorothiazide, buthiazide, chlorothalidone, cyclopenthiazide, cyclothiazide, ethiazide, fenquizone, hydrochlorothiazide, hydroflumethiazide, indapamide, methyclothiazide, metolazone, paraflozamide, polythiazide, quinethazone, teclothiazide, trichlormethiazide, aminomteradine, amiloride, Biogen BG 9719, chlorazanil, ethacrynic acid, etozolin, isosorbide, Kiowa Hakko KW 3902, mannitol, muzolimine, perhexiline, Sanofi-Aventis SR 121463, ticrynafen, triamterene, and urea.

23. The method of Claim 21, wherein the second agent comprises at least one diuretic which is an aldosterone antagonist.

24. A method for improving, or inhibiting decline in, exercise capacity in a subject having IPF, the method comprising administering to the subject a therapeutically effective amount of a selective ET<sub>A</sub> receptor antagonist, wherein the subject at baseline exhibits a 6MWD not greater than about 450 m.

25. The method of Claim 24, that is further effective to provide a reduction of at least about 25% in probability of a clinical worsening event during treatment, by comparison with placebo.

26. The method of Claim 24, that is further effective to inhibit worsening of or to ameliorate quality of life and/or dyspnea in the subject.

27. The method of Claim 24, wherein the subject at baseline has zero to about 5% honeycombing.

28. The method of Claim 24, wherein the subject at baseline has greater than about 3.3% honeycombing.

29. The method of Claim 24, wherein the subject at baseline has a clinical diagnosis of IPF, the diagnosis having been made without surgical lung biopsy.

30. The method of Claim 24, wherein the diagnosis has been made with the aid of HRCT.
31. The method of Claim 24, wherein the selective ET\textsubscript{A} receptor antagonist has an ET\textsubscript{A}/ET\textsubscript{B} selectivity ratio of at least about 500 by the Greene method.

32. The method of Claim 24, wherein the selective ET\textsubscript{A} receptor antagonist comprises at least one agent selected from the group consisting of ambrisentan, atrasentan, avosentan, BMS 193884, BQ-123, CI-1020, clazosentan, darusentan, edonentan, S-0139, sitaxsentan, TA-0201, TBC 3711, YM-598, ZD-1611, and ZD-4054.

33. The method of Claim 24, wherein the selective ET\textsubscript{A} receptor antagonist comprises ambrisentan.

34. The method of Claim 33, wherein the ambrisentan is administered in a daily dosage amount of about 1 mg to about 25 mg.

35. The method of Claim 24, wherein the selective ET\textsubscript{A} receptor antagonist comprises darusentan.

36. The method of Claim 35, wherein the darusentan is administered in a daily dosage amount of about 1 mg to about 600 mg.

37. The method of Claim 24, wherein the selective ET\textsubscript{A} receptor antagonist is administered as a first agent in combination therapy with a second agent effective for treatment of IPF or PH or a condition associated with IPF and or PH.

38. A method for treating IPF in a subject, the method comprising (a) diagnosing IPF without surgical lung biopsy; and (b) if IPF is so diagnosed, administering to the subject a therapeutically effective amount of a selective ET\textsubscript{A} receptor antagonist, wherein said administration is initiated not more than about 2 years after said diagnosis.

39. The method of Claim 38, wherein the diagnosis is made with the aid of HRCT.

40. The method of Claim 38, that is effective to provide a reduction of at least about 25% in probability of a clinical worsening event during treatment, by comparison with placebo.

41. The method of Claim 38, that is effective to inhibit worsening of or to ameliorate quality of life and/or dyspnea in the subject.

42. The method of Claim 38, wherein the subject at baseline has zero to about 5% honeycombing.
43. The method of Claim 38, wherein the subject at baseline has greater than about 3.3% honeycombing.

44. The method of Claim 38, wherein the subject additionally has PH at baseline.

45. The method of Claim 38, wherein the selective ET\textsubscript{A} receptor antagonist has an ET\textsubscript{A}/ET\textsubscript{B} selectivity ratio of at least about 500 by the Greene method.

46. The method of Claim 38, wherein the selective ET\textsubscript{A} receptor antagonist comprises at least one agent selected from the group consisting of ambrisentan, atrasentan, avosentan, BMS 193884, BQ-123, CI-1020, clazosentan, darusentan, edonentan, S-0139, sitaxsentan, TA-0201, TBC 3711, YM-598, ZD-1611, and ZD-4054.

47. The method of Claim 38, wherein the selective ET\textsubscript{A} receptor antagonist comprises ambrisentan.

48. The method of Claim 47, wherein the ambrisentan is administered in a daily dosage amount of about 1 mg to about 25 mg.

49. The method of Claim 38, wherein the selective ET\textsubscript{A} receptor antagonist comprises darusentan.

50. The method of Claim 49, wherein the darusentan is administered in a daily dosage amount of about 1 mg to about 600 mg.

51. The method of Claim 38, wherein the selective ET\textsubscript{A} receptor antagonist is administered as a first agent in combination therapy with a second agent effective for treatment of IPF or PH or a condition associated with IPF or PH.

52. A method for improving, or inhibiting decline in, pulmonary condition in a subject having IPF and PH, the method comprising administering to the subject a therapeutically effective amount of an endothelin receptor antagonist.

53. The method of Claim 52, wherein pulmonary condition is measured by one or more of a pulmonary function test, exercise capacity or a dyspnea index.

54. The method of Claim 52, that is further effective to provide a reduction of at least about 25% in probability of a clinical worsening event during treatment, by comparison with placebo.
55. The method of Claim 52, that is further effective to inhibit worsening of or to ameliorate quality of life in the subject.

56. The method of Claim 52, wherein the subject at baseline has zero to about 5% honeycombing.

57. The method of Claim 52, wherein the subject at baseline has greater than about 3.3% honeycombing.

58. The method of Claim 52, wherein the subject at baseline has a clinical diagnosis of IPF, the diagnosis having been made without surgical lung biopsy.

59. The method of Claim 58, wherein the diagnosis has been made with the aid of HRCT.

60. The method of Claim 52, wherein the endothelin receptor antagonist is a selective \( \text{ET}_A \) receptor antagonist having an \( \text{ET}_A/\text{ET}_B \) selectivity ratio of at least about 500 by the Greene method.

61. The method of Claim 52, wherein the endothelin receptor antagonist comprises at least one agent selected from the group consisting of ambrisentan, atrasentan, avosentan, bosentan, BMS 193884, BQ-123, CI-1020, clazosentan, darusentan, edonenton, S-0139, sitaxsentan, TA-0201, TBC 3711, YM-598, ZD-1611, and ZD-4054.

62. The method of Claim 52, wherein the endothelin receptor antagonist comprises ambrisentan.

63. The method of Claim 62, wherein the ambrisentan is administered in a daily dosage amount of about 1 mg to about 25 mg.

64. The method of Claim 52, wherein the endothelin receptor antagonist comprises darusentan.

65. The method of Claim 64, wherein the darusentan is administered in a daily dosage amount of about 1 mg to about 600 mg.

66. The method of Claim 52, wherein the endothelin receptor antagonist is administered as a first agent in combination therapy with a second agent effective for treatment of IPF or PH or a condition associated with IPF or PH.
### A. CLASSIFICATION OF SUBJECT MATTER

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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 practical, search terms used)

EPO-Internal, WPI Data, BIOSIS, EMBASE

### 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.
- **E** earlier document but published on or after the international filing date.
- **L** document which may throw doubts on prior art claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified).
- **D** 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.

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

**A** document member of the same patent family.

**Date of the actual completion of the international search**

27 January 2010

**Date of mailing of the international search report**

25/02/2010

**Name and mailing address of the ISA/**

European Patent Office, P B 5818 Patentlaan 2
NL- 2280 HV Rijswijk
Tel (+31-70) 340-2040,
Fax (+31-70) 340-3016

**Authorized officer**

TuIlberg, Erik
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Continuation of Box II.2

Claims Nos.: –

The present application does not fulfill the requirement of Article 6 PCT. The expression selective ETα receptor antagonist according to the subject-matter of claims 1, 10-12, 20, 21, 24, 31, 37, 38, 45, 51 and 60 is not clear because it is not unambiguously derivable for the skilled person which compounds fall within or without of the expression. It has therefore been interpreted in light of claims 13, 14, 17, 32, 33, 35, 46, 47 and 49 of the present application.

The subject-matter of claims 12, 31, 45 and 60 does not fulfill the requirements of Article 6 PCT because the expression "Greene Method" does not appear to relate to a method that is well recognized in the art.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.2), should the problems which led to the Article 17(2)PCT declaration be overcome.
# INTERNATIONAL SEARCH REPORT

**Box No. II** Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. **Claims Nos.**
   - because they relate to subject matter not required to be searched by this Authority, namely:

2. **Claims Nos.**
   - because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
     - see FURTHER INFORMATION sheet PCT/ISA/210

3. **Claims Nos.**
   - because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 64(a)

**Box No. III** Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. **As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.**

2. **As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.**

3. **As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.**

4. **No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims, it is covered by claims Nos.**

**Remark on Protest**

- The additional search fees were accompanied by the applicant's protest and where applicable, the payment of a protest fee
- The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation
- No protest accompanied the payment of additional search fees

Form PCT/ISA/210 (continuation of first sheet (Z)) (April 2005)
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