Treatment of early stage idiopathic pulmonary fibrosis

The present invention relates to the use of endothelin receptor antagonists (hereinafter ERA) for the treatment of early stage idiopathic pulmonary fibrosis (hereinafter early stage IPF or early IPF).

Idiopathic pulmonary fibrosis (IPF), also known as cryptogenic fibrosing alveolitis, is a distinct clinical disorder belonging to the spectrum of interstitial lung diseases (ILD). IPF is a progressive disease characterized by the presence of a histological pattern of usual interstitial pneumonia (UIP) on surgical lung biopsy. IPF was used to be considered as a chronic inflammatory disease resulting in parenchymal fibrosis. However, recent evidence suggests a mechanism of abnormal wound healing, with progressive extracellular matrix accumulation, decreased fibroblast-myoblast cell death, continuous epithelial cell apoptosis and abnormal re-epithelialization. Progressive fibrotic tissue deposition in the interstitial areas of the lung leads to decreased lung compliance and reduced gas exchanges.

The onset of symptoms is usually gradual and patients complain of non-productive cough, shortness of breath occurring first on exercise and then at rest. Cyanosis, cor pulmonale, and peripheral edema may be observed in the late phase of the disease.

In the presence of a surgical lung biopsy showing the histological appearance of UIP, the definite diagnosis of IPF requires the following (American Thoracic Society. Idiopathic pulmonary fibrosis: diagnosis and treatment. International consensus statement. American Thoracic Society (ATS) and the European Respiratory Society (ERS). Am J Respir Crit Care Med 2000; 161:646-64):

1) The exclusion of other causes of ILD,
2) Abnormal pulmonary function studies that include evidence of restriction of lung capacity and/or impaired gas exchange or decreased diffusing capacity for carbon monoxide (DLCO),
3) Abnormalities on conventional chest radiograph or high-resolution computed tomography (HRCT) scans.

The criteria for diagnosis of IPF in the absence of a surgical lung biopsy necessitate the correlation between all clinical and radiological features.

According to LeadDiscovery (2006), Idiopathic pulmonary fibrosis (hereinafter IPF) is a devastating, relentlessly progressive and lethal disease for which current therapy is minimally effective.

Precise figures for prevalence and incidence of IPF have not been reported. Prevalence was thought to be between 3 and 6 cases per 100,000 but could be as high as 13 to 20 cases per 100,000. Prevalence is higher in older adults (two-thirds of patients are over 60 years of age) and in males. The median survival after the diagnosis of biopsy-confirmed IPF is less than 3 years.

No therapies have been shown to improve survival or quality of life for patients with IPF. Current treatment is still based on the former presumption that IPF is an inflammatory process with concurrent remodeling of the lung by fibrosis. Consequently, it involves anti-inflammatory therapy, including corticosteroids, immunosuppressive/cytotoxic agents (e.g. azathioprine, cyclophosphamide) or a combination of both. However, because of the marginal benefit and serious side effects of the current therapies, along with newer insights into the pathogenesis of IPF, novel therapeutic approaches are highly needed. Antifibrotic therapy is aimed at decreasing matrix deposition or increasing collagen breakdown and a number of agents including colchicine, D-penicillamine, interferon gamma, and pirfenidone are currently under investigation. Lung transplantation has emerged as a viable option for some patients with IPF.

The neurohormone endothelin-1 (ET-1) belongs to a family of 21-amino-acid peptides released from the endothelium and is one of the most potent vasoconstrictors known. ET-1 can also promote fibrosis, cell proliferation, and remodeling, and is pro-inflammatory. ET-1 can modulate matrix production and turnover by altering the metabolism of fibroblasts to stimulate collagen synthesis or decrease interstitial collagenase production. Activation of the paracrine lung ET system has been confirmed in animal models of pulmonary fibrosis. ET-1 has also been linked to IPF in humans. In patients with IPF, ET-1 is increased in airway epithelium, and type II pneumocytes, compared with control subjects and with patients with nonspecific fibrosis.
Thus ET-1 could be a major player in the pathogenesis of IPF.

High Resolution Computer Tomography (HRCT) as well as classical computer tomography (CT) are to date together with pulmonary function tests the best non invasive tools to assess the extent of the disease and to attempt to delineate its stage of progression. Typically IPF at start of the disease will mainly show on CT scan ground-glass attenuation with little or no honeycomb. Ground-glass attenuation corresponds histologically to patchy alveolar septal fibrosis, air space 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 the destruction of the lung with dilatation of bronchioles that communicate with proximal airways. Honeycomb lesions tend to enlarge slowly over time (King Jr. TE. Idiopathic interstitial pneumonias in Interstitial Lung Disease fourth edition pages 701 786 Schwartz, King editors 2003 BC Decker Inc Hamilton-London).

Honeycomb can be semi-quantitated on HRCT at the lobe level or zones with scales from 0 to 5 or 0 to 100 with increments of 5 (Lynch DA et al. Am J Respir Crit Care Med 2005 172 488-493; Akira M, et al Idiopathic pulmonary fibrosis: progression of honeycombing at thin-section CT Radiology 1993 189: 687-691).

Early stage of IPF can be at best characterized by the presence of no or little honeycomb on HRCT or CT scans, as well as the presence of ground-glass in one or both lungs but not limited to these features. Early stage of IPF can be more accurately defined as IPF associated with no or low honeycomb at time of disease diagnosis. In rare cases the HRCT will not show ground-glass attenuation and/or honeycomb and/or reticulation. However, early IPF may also be diagnosed by other usual diagnostic tools but not limited to, such as magnetic resonance imaging, broncho-alveolar lavage, lung biopsy for histological assessment (e.g. surgical, transbronchial, or via mediastinoscopy).

Additionally, early IPF may also be diagnosed by cardio-pulmonary exercise test.

Despite low or no honeycomb visible on HRCT scan, honeycomb still may be seen on histological sections.

The term “low honeycomb” or “little honeycomb” means that honeycomb is present in less than 25% of the overall lung fields. In a further embodiment, the term “low honeycomb” or “little honeycomb” means that honeycomb is present in less than 10% of the overall lung fields.

According to LeadDiscovery (2006), diagnosing patients with early-stage IPF remains a great challenge.

Bosentan (Tracleer®) is an oral treatment for PAH (Class III and IV in the United States, Class III in Europe). Bosentan is a dual endothelin receptor antagonist with affinity for both endothelin ET_A and ET_B receptors thereby preventing the deleterious effects of ET-1. Bosentan competes with the binding of ET-1 to both ET_A and ET_B receptors with a slightly higher affinity for ET_A receptors (Ki = 4.1–43 nM) than for ET_B receptors (Ki = 38–730 nM).

In a clinical study (BUILD-1), the efficacy of bosentan in patients suffering from idiopathic pulmonary fibrosis (IPF) was evaluated in 2003. The studies did not show an effect on the primary endpoint of exercise capacity. However, bosentan showed efficacy on secondary endpoints related to death or disease worsening, providing strong rationale for Phase III mortality/morbidity study in IPF.

Full analysis of the BUILD-1 study presented at the American Thoracic Society (ATS) conference (23.05.2006) included evaluating the treatment effect of bosentan in patients who had lung biopsy (n=99) as a proof of IPF. The BUILD-1 findings in lung-biopsy proven IPF are unexpected, and warrant further clinical evaluation of bosentan in this indication. A phase III mortality and morbidity study in patients with biopsy proven IPF (BUILD-3 study) started by the end of 2006 and is currently ongoing.

WO 2004/105684 describes the use of a combination of NAC, SAPK and bosentan for IPF. However, early stage IPF is not mentioned in the publication.

WO 2005/110478 describes the use of a combination of pirfenidone or a pirfenidone analog and bosentan for IPF. Additionally, WO 2005/110478 describes the use of a combination of IFN-gamma and bosentan for IPF. However, early stage IPF is not mentioned in the publication.

Surprisingly, we found that this efficacy of bosentan was restricted to patients with early stage IPF. Thus, bosentan is useful for the treatment of early stage IPF. Further tests that have been carried out demonstrate that other ERA's are also useful for the treatment of early stage IPF.

The present invention relates to the use of an endothelin receptor antagonist, or a pharmaceutical composition comprising an endothelin receptor antagonist and either pirfenidone or interferon-gamma, for the preparation of a medicament for the treatment of early stage idiopathic pulmonary fibrosis.

A further embodiment of the present invention relates to the above-described use wherein the endothelin receptor antagonist is a dual endothelin receptor antagonist or a mixed endothelin receptor antagonist.

A further embodiment of the present invention relates to the above-described use wherein the endothelin receptor antagonist is a selective endothelin receptor antagonist that binds selectively to the ET_A receptor.

A further embodiment of the present invention relates to the above-described use wherein the endothelin receptor antagonist is a selective endothelin receptor antagonist that binds selectively to the ET_B receptor.

A further embodiment of the present invention relates to the above-described use wherein the endothelin receptor antagonist is selected from table 1.

A further embodiment of the present invention relates to the above-described use wherein the endothelin receptor antagonist is selected from darusentan, ambrisentan, atrasentan, sitaxsentan, avosentan, TBC-3711, tezosentan, clazosentan, propyl-sulfamic acid {5-(4-bromo-phenyl)-6-[2-(5-bromo-pyrimidin-2-yloxy)-ethoxy]-pyrimidine-4-yl}-amide and bosentan.

A further embodiment of the present invention relates to the above-described use wherein the endothelin receptor antagonist is selected from darusentan, ambrisentan, sitaxsentan, avosentan, TBC-3711, propyl-sulfamic acid {5-(4-bromo-phenyl)-6-[2-(5-bromo-pyrimidin-2-yloxy)-ethoxy]-pyrimidine-4-yl}-amide and bosentan.

A further embodiment of the present invention relates to the above-described use wherein the endothelin receptor antagonist is bosentan.

A further embodiment of the present invention relates to the above-described use wherein honeycomb on HRCT or CT scans is either absent or minimal.

A further embodiment of the present invention relates to the above-described use wherein honeycomb on HRCT or CT scans is present in less than 25% of the overall lung fields.

A further embodiment of the present invention relates to the above-described use wherein honeycomb on HRCT or CT scans is present in less than 10% of the overall lung fields.

A further embodiment of the present invention relates to the above-described use wherein the ground-glass attenuation could be any percentage between above zero to 80 % of lung fields.

A further embodiment of the present invention relates to the above-described use wherein bosentan is given to a patient at a daily dosage of 125 mg with or without a lower starting dose.

A further embodiment of the present invention relates to the above-described use wherein bosentan is given to a patient at a daily dosage of 250 mg with or without a lower starting dose.

The present invention relates to the use of an endothelin receptor antagonist alone or in combination with interferon-gamma (e.g. interferon gamma-1b) or pirfenidone for the preparation of a medicament for the treatment of early stage IPF.

Pirfenidone and interferon-gamma (e.g. interferon gamma-1b) can be purchased from commercial suppliers or synthesized according to methods in the art.

Early stage of IPF can be delineated as a stage of the disease at which honeycomb on HRCT or CT scans is either absent or minimal. In an embodiment of the invention the honeycomb is present in less than 10% of the overall lung fields. In a preferred embodiment the honeycomb, when expressed in a 0 to 100% scale, is present in less than 8%, or less than 5%, or less than 3%, or less than 2% of the overall lung fields. Most preferred the honeycomb is present in less than 1% of the overall lung fields. In a further embodiment the honeycomb, when expressed in a 1 to 5 scale, is present in less than a score of 3, preferably less than a score of 2, most preferred less than a score of 1.

An additional feature is the presence of ground-glass attenuation in one or both lungs fields but not limited to these features. Ground-glass extent in early IPF could be any percentage between above zero to 80 %, preferably more than 2% to up to 80% of lung fields (Akira M, et al Idiopathic pulmonary fibrosis: progression of honeycombing at thin-section CT Radiology 1993 189: 687-691).

When IPF cannot yet with high certainty be diagnosed by clinical/radiological features expressed in the ATS/ERS consensus guidelines, typically a lung biopsy is performed to either rule out or confirm early stage IPF (reference: American Thoracic Society. Idiopathic pulmonary fibrosis: diagnosis and treatment. International consensus statement. American Thoracic Society (ATS) and the European Respiratory Society (ERS). Am J Respir Crit Care Med 2000; 161:646-64).

Endothelin Receptor Antagonists (ERA):

Endothelin receptor antagonists, as defined above, encompass a wide range of structures and are useful alone or in the combinations and methods of the present invention. Nonlimiting examples of endothelin receptor antagonists that may be used in the present invention include those endothelin receptor antagonists as disclosed below. The endothelin receptor antagonist references identified below are incorporated herein in their entirety.

Endothelin-1 is a potent endogenous vasoconstrictor and smooth-muscle mitogen that is overexpressed in the plasma and lung tissue of patients with pulmonary arterial hypertension and pulmonary fibrosis. There are two classes of endothelin receptors: ET_A receptors and ET_B receptors, which play significantly different roles in regulating blood vessel diameter. In chronic pathological situations, the pathological effects of ET-1 can be mediated via both ET_A and ET_B receptors.

Two types of ERAs have been developed: dual ERAs, which block both ET_A and ET_B receptors, and selective ERAs, which block only ET_A receptors.

Dual Endothelin Receptor Antagonist (also called mixed Endothelin Receptor Antagonist) block both the ET_A and ET_B receptors. Bosentan (Tracleer®) is the first FDA approved ERA (see US 5,292, 740 or US 5,883,254; incorporated herein in its entirety by reference thereto).

Selective ERAs bind to the ET_A receptor in preference to the ET_B receptor. Currently, there are selective ERAs in clinical trials, such as sitaxsentan, atrasentan, avosentan, ambrisentan (BSF 208075), and TBC3711.

The synthesis of Ambrisentan is described in US 5,932,730 and US 5,969,134.

The synthesis of propyl-sulfamic acid {5-(4-bromo-phenyl)-6-[2-(5-bromo-pyrimidin-2-yloxy)-ethoxy]-pyrimidine-4-yl}-amide is described in WO 2002/53557.

Table 1

Endothelin Receptor Antagonists

COMPOUNDS AND COMPOUND CLASSES	REFERENCE/MANUFACTURER
bosentan	U.S. Pat. No. 5,883,254; (CAS No. 157212-55-0); Roche Holding AG, Actelion, Genentech
sitaxsentan	U.S. Pat. No. 5,594,021; (CAS No. 184036-34-8); ICOS-Texas Biotechnology, L.P.
darusentan	WO 99/16446; (CAS No. 221176-
BMS-187308	Bristol-Meyers Squibb; Clin. Cardiol. Vol. 23, Oct. 2000.
BMS-193884	Bristol-Meyers Squibb; Pharmacotherapy 22(1): 54--65, 2002.

Endothelin Receptor Antagonists

COMPOUNDS AND COMPOUND CLASSES	REFERENCE/MANUFACTURER
BMS-20794	Bristol-Meyers Squibb; Pharmacotherapy 22(1): 54--65, 2002.
BSF-208075; ambrisentan	Abbott Laboratories, Myogen, Inc.
CGS-27830	Novartis; Pharmacotherapy 22(1): 54--65, 2002.
IRL-3630	Novartis; Pharmacotherapy 22(1): 54--65, 2002.
IRL-1038	
enrasentan	SmithKline Beecham
FR-139317	Fujisawa Pharmaceutical Co, Ltd.; Pharmacotherapy 22(1): 54--65, 2002.
J-104121	Merck/Banyu; Pharmacotherapy 22(1): 54--65, 2002.
J-104132	Merck/Banyu; Pharmacotherapy 22(1): 54--65, 2002.
EMD-94246	Merck; Pharmacotherapy 22(1): 54--65, 2002.
L-744453	Merck; Pharmacotherapy 22(1): 54--65, 2002.
L-749329	Merck; Pharmacotherapy 22(1): 54--65, 2002.
L-753037	Merck; Pharmacotherapy 22(1): 54--65, 2002.
L-754142	Merck; Pharmacotherapy 22(1): 54--65, 2002.
LU135252	Knoll AG; Pharmacotherapy 22(1): 54--65, 2002.
LU208075	Knoll AG; Pharmacotherapy 22(1): 54--65, 2002.
LU302146	Knoll AG; Pharmacotherapy 22(1): 54--65, 2002.
LU224332	Knoll AG; Pharmacotherapy 22(1): 54--65, 2002.
LU302872	Knoll AG; Pharmacotherapy 22(1): 54--65, 2002.
PD-142893	Parke-Davis; Pharmacotherapy 22(1): 54--65, 2002.
PD-145065	Parke-Davis; Pharmacotherapy 22(1): 54--65, 2002.
PD-147953	Parke-Davis; Pharmacotherapy 22(1): 54--65, 2002.
PD-156123	WO95/05376
RO46-2005	Hoffmann-La Roche; Pharmacotherapy 22(1): 54--65, 2002.
RO47-0203	Hoffmann-La Roche; Pharmacotherapy 22(1): 54--65, 2002.
RO 48-5695	Hoffmann-La Roche; Pharmacotherapy 22(1): 54--65, 2002.
RO 61-1790	Hoffmann-La Roche; Pharmacotherapy 22(1): 54--65, 2002.
RO-61-0612	Roche; Clin. Cardiol. Vol. 23, Oct. 2000.
SB-209670	SmithKline Beecham; Pharmacotherapy 22(1): 54--65, 2002.
SB-217242	SmithKline Beecham; Pharmacotherapy 22(1): 54--65, 2002.
SB-234551	SmithKline Beecham; Pharmacotherapy 22(1): 54--65, 2002.
SB-247083	SmithKline Beecham; Pharmacotherapy 22(1): 54--65, 2002.

Endothelin Receptor Antagonists

COMPOUNDS AND COMPOUND CLASSES	REFERENCE/MANUFACTURER
TA-0115	Tanabe Seiyaku Co.; Pharmacotherapy 22(1): 54--65, 2002.
TA-0201	Tanabe Seiyaku Co.; Pharmacotherapy 22(1): 54--65, 2002.
TBC11251	Texas Biotechnology Co.; Pharmacotherapy 22(1): 54--65, 2002.
TBC-3711	Texas Biotechnology Co.
TBC-11251	Texas Biotechnology Co.; Clin. Cardio. Vol. 23, Oct. 2000.
ZD 1611	Zeneca Group plc.; Pharmacotherapy 22(1): 54--65, 2002.
Sulphisoxazole (4-Amino-N-(3,4-dimethyl-5-isoxazolyl) benzenesulfonamide)	(CAS No. 127-69-5), Biochem. Biophys. Res. Comm. 201 228
Sulfonamide derivatives	WO 01/049685; Texas Biotechnology Corp.
3-Sulfamoyl-pyrazole derivatives	EP 1072597; Pfizer Ltd.
Biphenyl isoxazole sulfonamide compounds	U.S. Pat. No. 6,313,308, WO 00/056685; Bristol Myers Squibb Co.
4-Heterocyclyl-sulfonamidyl-6-methoxy-5-(2-methoxyphenoxy)-2-pyridyl-pyrimidine derivatives and their salts	WO 00/052007; Hoffmann LaRoche & Co.
3-acylamino-propionic acid and 3-sulfonylamino-propionic acid derivatives	EP 1140867; BASF AG
Phenylsulfonamide derivatives and their salts	U.S. Pat. No. 6,107,320; Bristol-Myers Squibb Co.
Pyrrole derivatives and their acid and alkali salts	JP 2000063354, Sumitomo Seiyaku, KK
Furanone and thiophenone derivatives	U.S. Pat. No. 6,017,916; Warner Lambert Co.
Pyrimidyl sulfonamide derivatives	EP 959072; Tanabe Seiyaku Co.
Pyrimidyl sulfonamide derivatives	EP 959073; Tanabe Seiyaku Co.
Benzothiazine derivatives, their acid addition and base salts	GB 2337048; Warner Lambert Co.
Phenyl isoxazole sulfonamide derivatives, their enantiomers, diastereomers and salts	U.S. Pat. No. 5,939,446; Bristol-Myers Squibb Co.
5-benzodioxolyl-cyclopentenopyridine derivatives, including 5-(2,2-Difluoro-1,3-benzodioxol-5-yl) cyclopentenopyridine derivatives and (5S, 6R, 7R)-6-carboxy-5-(2,2-difluoro-1,3-benzodioxol-5-yl)-7-(2-(3-hydroxy-2-methylpropyl)-4-methoxyphenyl)-2-N-isopropylaminocyclopentene (1, 2-b)pyridine	EP 1049691, Banyu Pharm Co. Ltd.
Amino acid derivatives and their salts including (R-(R*, S*))-gamma-((3-(1H-indol-3-yl)-2-methyl-1-oxo-2-(((tricyclo(3.3.1.13,7)dec-2-yloxy)carbonyl)amino) propyl)amino)-benzenepentanoic acid	U.S. Pat. No. 5,922,681; Warner Lambert Co.
15-ketoprostaglandin E	U.S. Pat. No. 6,197,821, EP 978284; R-

Endothelin Receptor Antagonists

COMPOUNDS AND COMPOUND CLASSES	REFERENCE/MANUFACTURER
compound provided that it does not contain an alpha bonded 8C or more backbone, including 13,14-dihydro-15-keto-16,16-difluoro-18S-methylprostaglandin E1	Tech Ueno Ltd.
Pyridyl-thiazole derivatives	U.S. Pat. No. 5,891,892; Warner Lambert Co.
Pyrrolidine and piperidine derivatives, their analogues and salts	U.S. Pat. No. 6,162,927, EP 1003740; Abbott Laboratories
Pyrrolidine carboxylic acid derivatives, their salts and stereoisomers	U.S. Pat. No. 6,124,341, EP 991620; Abbott Laboratories
Biphenyl derivatives of formula (I), their enantiomers, diastereomers, and salts	U.S. Pat. No. 5,846,965; Bristol-Myers Squibb Co.
Compound S-19777 of formula (I)	JP 10306087; Sankyo Co. Ltd.
Sulphonamide derivatives of formula (I) and their salts	JP 10194972; Tanabe Seiyaku Co.
Prostanoic acid derivative with an alpha-chain of at least 8 skeletal C	U.S. Pat. No. 6,242,485, EP 857718; R-Tech Ueno Ltd.
Aminoalkoxy or sulpho-alkoxy furan-2-ones or thiophen-2-ones, all of formula (I), and their salts	U.S. Pat. No. 6,133,263, WO 9737986; Warner Lambert Co.
Aminoalkoxy 5-hydroxyfuran-2-ones, their aminoalkylamino and alkyl-sulphonic acid analogues, all of formula (I), their tautomeric open-chain keto-acid forms, and their salts	U.S. Pat. No. 6,297,274, WO 9737985, Warner Lambert Co.
Pyrrolidine derivatives	EP 888340; Abbott Laboratories
Phenylalanine derivatives of formula (I)	U.S. Pat. No. 5,658,943; Warner Lambert Co.
N-isoxazolyl-biphenylsulphonamide derivatives of formula (I) and their salts, including N-(3,4-di methyl-5-isoxazolyl)-2'-(hydroxymethyl) (1,1'-bi phenyl)-2-sulphonamide	U.S. Pat. No. 6,271,248, U.S. Pat. No. 6,080,774, EP 768305; Bristol-Myers Squibb Co.
3-Aryl (or cycloalkyl) 5H-furan-2-ones of formula (I) and their salts, solvates, and hydrates	U.S. Pat. No. 5,998,468, WO 9708160; Warner Lambert Co.
N-Isoxazolyl-4'-heterocyclyl(alkyl)-1,1'-biphenyl-2-sulphonamides of formula (I) and their enantiomers, diastereomers and salts	U.S. Pat. No. 5,612,359; Bristol-Myers Squibb Co.
Thieno(2,3-d) pyrimidine derivatives (I) contg. a carboxyl gp. or ester and a gp. other than carboxyl which is capable of forming an anion or a gp. convertible to it	U.S. Pat. No. 6,140,325, EP 846119; Takeda Chem. Ind. Ltd.
2(5H)-Furanone derivatives of formula (I) and their salts	U.S. Pat. No. 5,922,759, U.S. Pat. No. 6,037,951, WO 9702265; Warner Lambert Co.
Heterocyclic pyridine sulphonamide derivatives of formula (I) and their N oxides, salts and prodrugs	U.S. Pat. No. 6,258,817, U.S. Pat. No. 6,060,475, U.S. Pat. No. 5866568, EP 832082; ZENECA LTD.

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COMPOUNDS AND COMPOUND CLASSES	REFERENCE/MANUFACTURER
Dihydropyridine carboxylic acid anhydride derivatives of formula (I) and their salts	U.S. Pat. No. 5,576,439; Ciba Geigy Corp.
N-pyrimidinyl-sulphonamide derivatives of formula (I) and their salts	U.S. Pat. No. 5,739,333, EP 743307; Tanabe Seiyaku Co.
Aroylamidoacyl di-C-substd. glycine derivatives of formula (I) and their salts	U.S. Pat. No. 5,977,075, EP 821670, Novartis AG
Benzothiazine dioxides of formula (I) and their salts	U.S. Pat. No. 5,599,811, EP 811001; Warner Lambert Co.
N-Isoxazolyl-4'-substd.-1,1'-biphenyl-2-sulphonamide derivatives of formula (I) and their enantiomers, diastereomers and salts	U.S. Pat. No. 5,760,038, EP 725067; Bristol-Myers Squibb Co.
4-Oxo-2-butenoic acid derivatives of formula (I) and 3-hydroxy-2(5H)-furanone derivatives of formula (II), and their salts	WO 9623773, JP 8523414; Banyu Pharm Co. Ltd.
Aza-aminoacids of formula (I)	ZA 9501743; Abbott Laboratories
Sulphonamides of formula (I) and their salts	U.S. Pat. No. 6,004,965, EP 799209; Hoffmann La Roche & Co.
Aryl compounds of formula (I) and their salts	U.S. Pat. No. 6,207,686, EP 792265; Fujisawa Pharm Co. Ltd.
Phenoxyphenylacetic acid derivatives and analogues of formula (I) and their salts	U.S. Pat. No. 5,559,135, WO 9608487; Merck & Co. Inc.
3- (and 5-) Benzene-sulphonamido-isoxazole derivatives of formula (I) and their salts	U.S. Pat. No. 5,514,696; Bristol-Myers Squibb Co.
Endothelin antagonists of formula (I) and their salts, esters and prodrugs	ZA 9500892; Abbott Laboratories
Phenoxyphenylacetic acid derivatives of formula (I) and their salts	U.S. Pat. No. 5,538,991, WO 9608486; Merck & Co. Inc.
N-Isoxazolyl-4-heteroar(alk)yl-biphenyl-2-sulphonamide derivatives of formula (I) and their enantiomers, diastereomers and salts	EP 702012; Bristol-Myers Squibb Co.
Pyrrolidine and piperidine derivatives of formula (I) and their salts	U.S. Pat. No. 5,622,971, U.S. Pat. No. 5,731,434, U.S. Pat. No. 5,767,144, EP 776324; Abbott Laboratories
Peptide derivatives of formula (I) and their salts	U.S. Pat. No. 5,550,110, EP 767801; Warner Lambert Co.
Porphyrins of formula (I) or their metal complexes or salts	JP 7330601; Kowa Co. Ltd.
Triazine or pyrimidine derivatives of formula (I)	U.S. Pat. No. 5,840,722, EP 752854; BASF AG
Bicyclic piperazinone derivatives of formula (I) and their salts	DE 4341663; BASF AG
Benzenesulphonamide derivatives of formula (I), and their salts, including 4-tert-butyl-N-(5-(4-methylphenyl)-6-(2-(5-(3-thienyl)pyrimidin-2-yloxy)ethoxy)pyrimidin-4-yl)-benzenesulphonamide	U.S. Pat. No. 5,728,706, EP 658548; Tanabe Seiyaku Co.
RES-1214 of formula (I)	JP 7133254; Kyowa Hakko Kogyo
Bicyclic pyrimidine or 1,4-	U.S. Pat. No. 5,693,637, EP 733052, EP

Endothelin Receptor Antagonists

COMPOUNDS AND COMPOUND CLASSES	REFERENCE/MANUFACTURER
diazepine derivatives of formula (I) and their acid addn. salts	733052; BASF AG., Hoechst AG.
5,11-Dihydro-11-oxo-dibenzo(b,e) diazepine derivatives of formula (I)	U.S. Pat. No. 5,420,123; Bristol-Myers Squibb Co.
Diaryl- and aryloxy compounds of formula (I), their salts, N-oxides and prodrugs	U.S. Pat. No. 6,211,234, EP 728128; Rhone Poulenc Rorer Ltd.
Non-peptidic compounds incorporating a cyclobutane ring of formula (I) and their salts	U.S. Pat. No. 5,492,917, WO 9508989; Merck & Co. Inc.
Amino acid derivatives of formula (I) and their salts	WO 9508550; Abbott Laboratories
Substituted 2(5H) furanone, 2(5H) thiophenone and 2(5H) pyrrolone derivatives of formula (I) and their salts	EP 714391; Warner Lambert Co.
Cyclopentene derivatives of formula (I) and their salts	U.S. Pat. No. 5,714,479, EP 714897; Banyu Pharm Co. Ltd.
Cyclopentane derivatives of formula (I) and their salts	WO 9505372; Banyu Pharm Co. Ltd.
Thienopyrimidine deriv. of formula (I) or one of its salts	EP 640606; Takeda Chem. Ind. Ltd., Takeda Pharm Ind. Co. Ltd.
Heteroaromatic ring-fused cyclopentene derivatives of formula (I), and their salts	U.S. Pat. No. 5389620, U.S. Pat. No. 5714479, EP 714897; Banyu Pharm Co. Ltd.
Phenalkyl substd. phenyl compounds of formula (I) and their salts	U.S. Pat. No. 5,686,478, EP 710235; Merck & Co. Inc.
Benzimidazolinone compounds substd. with phenoxyphenylacetic acid derivatives of formula (I) and their salts	U.S. Pat. No. 5,391,566, WO 9503044; Merck & Co. Inc.
Triterpene derivatives of formula (I) and their salts	JP 6345716; Shionogi & Co. Ltd.
N-Acyl-N-(amino- or hydroxy-alkyl)-tripeptide derivatives of formula (I) and their salts	U.S. Pat. No. 5,888,972, EP 706532; Fujisawa Pharm Co. Ltd.
Naphthalenesulphonamido-isoxazoles of formula (I) and their salts	U.S. Pat. No. 5,378,715; Bristol-Myers Squibb Co.
Amino acid phosphonic acid derivatives of formula (I), their enantiomers, diastereoisomers, epimers and salts	U.S. Pat. No. 5,481,030, EP 639586; ADIR & CIE
Endothelin antagonist of formula (I) or its salts	U.S. Pat. No. 5,420,133; Merck & Co Inc
Peptide derivatives for formula (I) and their salts	WO 9419368; Banyu Pharm Co Ltd
Endothelin antagonist of formula (I) or its salts	U.S. Pat. No. 5,374,638; Merck & Co Inc.
Compounds of formula (I), and their salts	U.S. Pat. No. 5,352,800; Merck & Co. Inc.
1,4-Dihydro-4-quinolinones and related compounds of formula (I) and their isomers and salts	U.S. Pat. No. 5,985,894, EP 498721; Roussel-Uclaf, Hoechst Marion Roussel
Cyclic depsipeptide of formula (I)	GB 2266899; Merck & Co. Inc.
Condensed thiadiazole derivatives of formula (I) and their salts	U.S. Pat. No. 5,550,138, EP 562599; Takeda Chem. Ind. Ltd.
Compounds (I') and their salts	U.S. Pat. No. 5,550,138, EP 562599; Takeda Chem. Ind. Ltd.
Purified cyclic depsipeptide	U.S. Pat. No. 5,240,910; Merck & Co. Inc.

Endothelin Receptor Antagonists

COMPOUNDS AND COMPOUND CLASSES	REFERENCE/MANUFACTURER
endothelin antagonist of formula (I)	
Cochinmycins (IV) and (V)	U.S. Pat. No. 5,240,910; Merck & Co. Inc.
Peptide derivatives (I) or their salts	JP 5194592; Takeda Chem. Ind. Ltd.
Cyclic peptides (I) or salts thereof	JP 5194589; Takeda Chem. Ind. Ltd.
Peptides of formula (I) and their salts	U.S. Pat. No. 5,614,497, EP 552489; Takeda Chem. Ind. Ltd.
Cyclic hexapeptide derivatives of formula (I) and their salts, including cyclo-(D-Asp-Trp-Asp-D-Leu-Leu-D-Trp) (Ia)	EP 552417; Takeda Chem. Ind. Ltd.
Indane and indene derivatives of formula (I) and their salts	EP 612244; Smithkline Beecham Corp.
Cyclic peptide derivatives of formula (I) and their salts	U.S. Pat. No. 5,616,684, U.S. Pat. No. 5,883,075, EP 528312; Takeda Chem. Ind. Ltd.
Endothelin (ET) analogue peptides of formula (I) and their salts	U.S. Pat. No. 5,352,659, EP 499266; Takeda Chem. Ind. Ltd.
Cyclic depsipeptides of formula (A)	EP 496452, U.S. Pat. No. 4,810,692; Merck & Co. Inc.
N-((2'-(((4,5-dimethyl-3-isoxazolyl)amino)sulfonyl)-4-(2-oxazolyl) (1,1'-bi phenyl)-2-yl)methyl)-N,3,3-trimethylbutanamide and salts thereof	U.S. Pat. No. 6,043,265; Bristol-Myers Squibb Co.
N-(4,5-dimethyl-3-isoxazolyl)-2'-((3,3-dimethyl-2-oxo-1-pyrrolidinyl)methy 1)-4'-(2-oxazolyl) (1,1'-biphenyl)-2-sulfonamide, and salts thereof.	U.S. Pat. No. 6,043,265; Bristol-Myers Squibb Co.
Substituted biphenyl sulfonamide compounds of formula (I), their enantiomers and diastereomers, and pharmaceutically acceptable salts thereof	U.S. Pat. No. 5,780,473; Abbott Laboratories
Compounds of formula (I) and salts thereof, including intermediates in the process of preparation	U.S. Pat. No. 6,162,927; Abbott Laboratories
Heterocyclyl-substituted biphenylsulfonamide	U.S. Pat. No. 5,780,473
Crystalline sodium salt of 2-pyrimidinyloxy-3,3-diphenylpropionic acid derivative	WO 2001030767; BASF AG
Phenyl compounds substituted with heteroaryl (preferably thienyl methoxy) moieties and their derivatives	U.S. Pat. No. 6,124,343; Rhone-Poulenc Roses Ltd.
1,3-benzodioxole compounds	U.S. Pat. No. 6,048,893; Rhone-Poulenc Rorer Ltd.
Biphenyl sulfonamides of formula (I)	U.S. Pat. No. 1998-91847P, EP 1094816; Bristol-Myers Squibb Co.
Compound (I) or its salt	EP 950418; Takeda Chem Ind Ltd.
A carboxylic acid of formula (I) or (II), including s-triazinyl-or pyrimidinyl-substituted alkanoic acid derivative	EP 1014989; Knoll AG
Endothelin antagonist of	AU 739860; Knoll AG

Endothelin Receptor Antagonists

COMPOUNDS AND COMPOUND CLASSES	REFERENCE/MANUFACTURER
formula (I)	
N-(3,4-dimethyl-5-isoxazolyl)-4'-(2-oxazolyl)(1,1'-biphenyl)-2-sulphonamide and its salts	U.S. Pat. No. 5,916,907, U.S. Pat. No. 5,612,359; Bristol-Myers Squibb Co.
N-((2'-(((4,5-dimethyl-3-isoxazolyl) amino)sulphonyl)-4-(2-oxazolyl) (1,1'-biphenyl)-2-yl)methyl)-N,3,3-trimethyl butanamide and its salts	U.S. Pat. No. 5,916,907, U.S. Pat. No. 5,612,359; Bristol-Myers Squibb Co.
Pyrrolidine derivatives of formula (I) and their salts, including (2R,3R,4S)-2-(3-fluoro-4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(2-(N-propyl-N-pentanesulphonylamino)ethyl)-pyrrolidine-3-carboxylic acid	U.S. Pat. No. 1997-794506, EP 885215; Abbott Laboratories
Phenoxyphenylacetic acids and derivatives of the general structural formula I	U.S. Pat. No. 5,565,485; Merck & Co., Inc.
Compounds of the formula I, namely novel pyridine derivatives including N-(2-pyridyl)sulphonamides, and pharmaceutically-acceptable salts thereof	U.S. Pat. No. 5,641,793; Zeneca Limited
N-heterocyclic sulfonamides of the formula I, their pharmaceutically-acceptable salts, and pharmaceutical compositions containing them	U.S. Pat. No. 5,668,137; Zeneca Ltd.
Phenoxyphenylacetic acids and derivatives of the general structural formula I	U.S. Pat. No. 5,668,176; Merck & Co. Inc.
Compounds of Formula I and the pharmacologically acceptable salts thereof, including 2-benzo->1,3!dioxol-5-yl-4-(4-methoxyphenyl)-4-oxo-3-(3,4,5-trimethoxybenzyl)-but-2-enoic acid	U.S. Pat. No. 5,691,373; Warner-Lambert Company
Phenoxyphenylacetic acids and derivatives of general structural formula (I)	U.S. Pat. No. 5,767,310; Merck & Co., Inc.
N-heterocyclyl sulphonamide derivatives and their pharmaceutically acceptable salts	U.S. Pat. No. 5,861,401, U.S. Pat. No. 6,083,951; Zeneca Limited
Heterocyclic compounds of the formula I and salts thereof, including N-heterocyclyl sulphonamides	U.S. Pat. No. 5,866,568; Zeneca Limited
Pyrimidines of formula I	U.S. Pat. No. 5,883,254, 6,121,447, 6,274,734; Hoffmann-La Roche Inc.
Nonpeptide compounds of formula I	U.S. Pat. No. 6,017,916; Warner-Lambert Company
Ketoacid compounds of the formula I and pharmaceutically acceptable salts thereof.	U.S. Pat. No. 6,043,241; Warner-Lambert Company
1,2-diheteroethylene sulfonamides	U.S. Pat. No. 6,136,971; Roche Colorado Corporation
Compound of the formula (I) and salts or hydrates thereof	U.S. Pat. No. 6,218,427; Shionogi & Co., Ltd.
Peptides of the formula (I) and their salts	U.S. Pat. No. 6,251,861; Takeda Chemical Industries, Ltd.

Endothelin Receptor Antagonists

COMPOUNDS AND COMPOUND CLASSES	REFERENCE/MANUFACTURER
Substituted pyrazin-2-yl-sulphonamide (-3-pyridyl) compounds of formula I, salts, and pharmaceutical compositions containing them.	U.S. Pat. No. 6,258,817; Zeneca Ltd.
4,5-Dihydro-(1H)-benz(g)indazole-3-carboxylic acid derivatives of formula I and their salts	U.S. Pat. No. 6,291,485; Teikoku Hormone Mfg. Co., Ltd.
Nonpeptide endothelin I antagonists of formula I	U.S. Pat. No. 6,297,274; Warner-Lambert Company
Carboxylic acid derivatives of formula (I) and their salts, enantiomers and diastereomers	EP 946524; BASF AG
4'-Heterocyclyl(alkyl)-N-isoxazolyl-biphenyl-2-yl sulphonamides of formula (I), and their enantiomers, diastereoisomers, and salts	U.S. Pat. No. 5,846,990; BRISTOL-MYERS SQUIBB CO
Biphenyl sulfonamides of formula (I)	WO 200001389; BRISTOL-MYERS SQUIBB CO
Endothelin antagonist of formula (I)	WO 9916444, EP 1019055; KNOLL AG
Endothelin antagonist of formula (I)	DE 19743140; KNOLL AG
Pyrrolidine derivatives of formula (I) and their salts	WO 9730045; ABBOTT Laboratories
Canrenoate Potassium	U.S. Pat. No. 5,795,909
Canrenone	U.S. Pat. No. 5,795,909
Dicirenone	U.S. Pat. No. 5,795,909
Mexrenoate Potassium	U.S. Pat. No. 5,795,909
Prorenoate Potassium	U.S. Pat. No. 5,795,909
4-amino-5-furyl-2-yl-4H-1,2,4-triazolethiol derivatives	Chinese Chemical Letters (2003), 14(8), 790--793.
3-alkylthio-4-arylideneamino-5-(2-furyl)-1,2,4-triazole derivatives	Chinese Chemical Letters (2003), 14(8), 790--793.
BMS-346567	Abstracts of Papers, 226th ACS National Meeting, New York, NY, September 7--11, 2003 (2003), MEDI-316.; Bristol-Myers Squibb
Alkanesulfonamides of formula I	WO2003055863
Benzo-fused heterocycles of formula I	WO 2003013545
(S*)-(4,6-dimethylpyrimidin-2-yloxy)-[(5S*)-2-oxo-5-phenyl-3-(2,4,6-trifluorobenzyl)-2,3,4,5-tetrahydro-1H-benzo[e][1,4]diazepin-5-yl]acetic acid	WO 2003013545
(S*)-(3,5-dimethoxyphenoxy)[(1S*)-1-phenyl-1,2,3,4-tetrahydroisoquinolin-1-yl] acetic acid	WO 2003013545
N-phenylimidazole derivatives	U.S. Pat. No. 2003004202; U.S. Pat. No. 2003153567; U.S. Pat. No. 6,620,826
Pyrimidine-sulfamides of formula I	WO 2002053557
Arylalkylsulfonamides of formulas I and II	WO 2002024665
Pyrimidino-pyridazines of formulas I and II	U.S. Pat. No. 2002061889; U.S. Pat. No. 6,670,362
Arylethenesulfonic acid pyrimidinylamides of formula I	U.S. Pat. No. 2003220359

Endothelin Receptor Antagonists

COMPOUNDS AND COMPOUND CLASSES	REFERENCE/MANUFACTURER
Mercaptopyrrolidine carboxamides related compounds of formula I	U.S. Pat. No. 2002049243; U.S. Pat. No. 6,541,638
(2S,4R)-4-mercapto-1-(naphthalene-2-sulfonyl)pyrrolidine-2-carboxylic acid methyl(o-tolylcarbamoylmethyl)amide	U.S. Pat. No. 2002049243; U.S. Pat. No. 6,541,638
N-aminocarbonyl-β-alanines of formula I	WO 2001060379
4-(4-pyrimidinyloxy)-2-butyn-1-ol derivatives of formulas I and II	U.S. Pat. No. 2003087920
Pyrimidinyloxypropionates of formula I	WO 2001005771
(S)-2-(4-methoxy-5-methylpyrimidin-2-yloxy)-3-methoxy-3,3-diphenylpropionic acid	WO 2001005771
2-pyrimidinyloxypropanoates and analogs thereof of formulas I and II	WO 2000073276
Pyrrolidinecarboxylates of formulas I and II	U.S. Pat. No. 6,124,341
N-(pyridylpyrimidinyl) heterocyclysulfonamides	U.S. Pat. No. 6,417,360
4-(heterocyclylsulfonamido)-5-(2-methoxyphenoxy)-2-phenyl derivatives of formula I	U.S. Pat. No. 6,242,601
Pyridylpyrimidines of formula I	U.S. Pat. No. 6,242,601
Monoarginiyl salts	U.S. Pat. No. 6,300359
(E)-3-{1-n-butyl-5-[2-(2-carboxyphenyl)methoxy-4-chlorophenyl]-1H-pyrazol-4-yl}-2-{(5-methoxy-2,3-dihydrobenzofuran-6-yl)methyl}-prop-2-enoic acid	U.S. Pat. No. 6,300359
3-carbamoylalkoxy-2-aryloxypropionates and analogs thereof of formula I	U.S. Pat. No. 6,509,341
Indole derivatives of formula I	U.S. Pat. No. 6,017,945; U.S. Pat. No. 6,136,843; U.S. Pat. No. 6,306,852; U.S. Pat. No. 2001014677; U.S. Pat. No. 6,384,070
α-hydroxy acid derivatives of formula I	U.S. Pat. No. 6,686,369
4-benzodioxolylpyrrolidine-3-carboxylates and analogs thereof of formula I	WO 9730046
Isoxazoles and imidazoles of formula I	U.S. Pat. No. 6,030,970; U.S. Pat. No. 6,174,906
Furan and thiopiene derivatives of formulas I and II	U.S. Pat. No. 6,017,952; U.S. Pat. No. 6,051,599
N-isoxazolylthiophenesulfonamides and analogs thereof of formulas I and II	U.S. Pat. No. 5,490,962; U.S. Pat. No. 5,516,680; U.S. Pat. No. 5,594,021; U.S. Pat. No. 5,962,490; U.S. Pat. No. 6,139,574; U.S. Pat. No. 6,342,610; U.S. Pat. No. 6,331,637; U.S. Pat. No. 6,514,518; U.S. Pat. No. 6,632,829
N-isoxazolyl(hetero) arenesulfonamides of formulas I and II	U.S. Pat. No. 5,571,821; U.S. Pat. No. 5,490,962; U.S. Pat. No. 5,464,853; U.S. Pat. No. 5,514,691; U.S. Pat. No. 5,516,680; U.S. Pat. No. 5,591,761; U.S. Pat. No. 5,594,021; U.S. Pat. No. 5962,490; U.S. Pat. No. 6,030,991; U.S. Pat. No. 6,139,574; U.S. Pat. No. 6,331,637; U.S. Pat. No. 6,376,523; U.S. Pat. No. 6,541,498; U.S. Pat. No. 6,514,518; U.S. Pat. No. 6,613,804
N-(4-pyrimidinyl)sulfonamides of formula I	EP 713875
Arylimidazolylpropenoates and related compounds of formula I	U.S. Pat. No. 2003153567; U.S. Pat. No. 6,620,826
(E)-3-[s-butyl-1-[2-[N-(phenylsulfonyl)]carboxamido-	U.S. Pat. No. 2003153567; U.S. Pat. No. 6,620,826

Endothelin Receptor Antagonists

COMPOUNDS AND COMPOUND CLASSES	REFERENCE/MANUFACTURER
4-methoxyphenyl]-1H-imidazol-5-yl}-2-[(2-methoxy-4,5-methylenedioxyphenyl)methyl]-2-propenoic acid dipotassium salt	
Pyrimidine and triazine derivatives of formulas I and II	U.S. Pat. No. 5,932,730; U.S. Pat. No. 6,197,958; U.S. Pat. No. 6,600,043
Indane and Indene derivatives of formula I	U.S. Pat. No. 6,271,399; U.S. Pat. No. 6,087,389; U.S. Pat. No. 6,274,737; U.S. Pat. No. 2002002177; U.S. Pat. No. 6,448,260
Heterocromatic ring-fused cyclopentene derivatives of formula I	U.S. Pat. No. 5,389,620; U.S. Pat. No. 5,714,479
(5RS,6SR,7RS)-6-carboxy-7-(4-methoxyphenyl)-5-(3,4-methylenedioxyphenyl)cyclopenteno[1,2-b]pyridine	U.S. Pat. No. 5,389,620; U.S. Pat. No. 5,714,479
Pyrido[2,3-d]pyrimidinesof formulas I and II	U.S. Pat. No. 5,654,309
Pyrido[2,3-d]pyrimidine-3-acetic acid of formula II	U.S. Pat. No. 5,654,309
4-Heterocyclyl-sulfonamidyl-6-methoxy-5-(2-methoxyphenoxy)-2-pyridyl-pyrimidine derivatives of formula I	WO 200052007
Alpha-hydroxy-carboxylic acid derivatives of formula I	DE 19614533
2-(4,6-dimethylpyrimidin-2-yloxy)-3,3-diphenylbutyric acid	DE 19614533
2-formylaniline derivatives of formula V	WO 2003080643
6a-{3-[2-(3-carboxy-acryloylamino)-5-hydroxyphenyl]-acryloyloxymethyl}-2,2,6b,9,9,12a-hexamethyl-10-oxo-1,3,4,5,6,6a,7,8,8a,9,9,12a,12b,13,14b-octadecahydro-2H-picene-4a-carboxylic acid or its salts	WO 2003080643
Alkanesulfonamides of formulas I or Ia	WO 2003055863
ethanesulfonic acid {6-[2-(5-bromo-pyrimidin-2-yloxy)-ethoxy]-5-para-tolyl-pyrimidin-4-yl}-amine	WO 2003055863
N-phenyl imidazole derivatives of formula I or salts thereof	U.S. Pat. No. 2003004202
(E)-3-[2-butyl-1-[2-(2-carboxyphenyl)methoxy-4-methoxy]phenyl-1H-imidazol-5-yl]-2-[(2-methoxy-4,5-methylenedioxyphenyl)methyl]-2-propenoic acid	U.S. Pat. No. 2003004202
Benzofused heterocycle derivatives of formula I and salts thereof	WO 2003013545

Also included in Table 1 are the following ERA's:

Atrasentan, avosentan, tezosentan, clazosentan and propyl-sulfamic acid {5-(4-bromo-phenyl)-6-[2-(5-bromo-pyrimidin-2-yloxy)-ethoxy]-pyrimidine-4-yl}-amide.

The amount of endothelin receptor antagonist that is administered and the dosage regimen for the methods of this invention also depend on a variety of factors, including the age, weight, sex and medical condition of the subject, the severity of the pathological condition, the route and frequency of administration, and the particular endothelin receptor antagonist employed, and thus may vary widely. A daily dose administered to a subject of about 0.001 to 100 mg/kg body weight, or between about 0.005 and about 60 mg/kg body weight, or between about 0.01 and about 50 mg/kg body weight, or between about 0.015 and about 15 mg/kg body weight, or between about 0.05 and about 30 mg/kg body weight, or between about 0.075 to 7.5 mg/kg body weight, or between about 0.1 to 20 mg/kg body weight, or between about 0.15 to 3 mg/kg body weight, may be appropriate.

The amount of endothelin receptor antagonist that is administered to a human subject typically will range from about 0.1 to 2400 mg, or from about 0.5 to 2000 mg, or from about 0.75 to 1000 mg, or from about 1 mg to 1000 mg, or from about 1.0 to 600 mg, or from about 5 mg to 500 mg, or from about 5.0 to 300 mg, or from about 10 mg to 200 mg, or from about 10.0 to 100 mg. The daily dose can be administered in one to six doses per day.

In a preferred embodiment, bosentan is administered at a daily dose to a subject of about 62.5 mg twice a day, or 125 mg twice a day to adult patients.

The endothelin receptor antagonists and their pharmaceutically usable salts can be used as medicament (e.g. in the form of pharmaceutical preparations). The pharmaceutical preparations can be administered internally, such as orally (e.g. in the form of tablets, coated tablets, dragées, hard and soft gelatine capsules, solutions, emulsions or suspensions), inhalations, nasally (e.g. in the form of nasal sprays) or rectally (e.g. in the form of suppositories). However, the administration can also be effected parenterally, such as intramuscularly or intravenously (e.g. in the form of injection solutions).

The endothelin receptor antagonists and their pharmaceutically usable salts can be processed with pharmaceutically inert, inorganic or organic adjuvants for the production of tablets, coated tablets, dragées, and hard gelatine capsules. Lactose, corn starch or derivatives thereof, talc, stearic acid or its salts etc. can be used, for example, as such adjuvants for tablets, dragées, and hard gelatine capsules.

Suitable adjuvants for soft gelatine capsules, are, for example, vegetable oils, waxes, fats, semi-solid substances and liquid polyols, etc. Suitable adjuvants for the

production of solutions and syrups are, for example, water, polyols, saccharose, invert sugar, glucose, etc.

Suitable adjuvants for injection solutions are, for example, water, alcohols, polyols, glycerol, vegetable oils.

Suitable adjuvants for suppositories are, for example, natural or hardened oils, waxes, fats, semi-solid or liquid polyols.

Moreover, the pharmaceutical preparations can contain preservatives, solubilizers, viscosity-increasing substances, stabilizers, wetting agents, emulsifiers, sweeteners, colorants, flavorants, salts for varying the osmotic pressure, buffers, masking agents or antioxidants. They can also contain still other therapeutically valuable substances.

Experimental Section / Biology:

The findings with bosentan can be extrapolated to other endothelin receptor antagonists as mentioned above, because endothelin-1 (ET-1) has been shown to play a central role in the development of fibrosis and therefore drugs used to target and inhibit the action of ET-1 will be effective in treating early fibrosis.

Indeed, at a whole body level, transgenic mice overexpressing ET-1 develop a phenotype of fibrosis (pulmonary and renal). This fibrosis is a direct consequence of ET-1 action, because there is no associated increase in blood pressure (1, 2). At a cellular and biochemical level also, endothelin is a central mediator of fibrosis (3). ET-1 induces chemotaxis and proliferation of fibroblasts, increases the synthesis and production of various extracellular matrix proteins like laminin, collagen, and fibronectin, while inhibiting collagenase activity. ET-1 also induces expression of other profibrotic factors, such as connective tissue growth factor and transforming growth factor beta (TGF-β). ET-1 also increases the pro-inflammatory effector, nuclear factor-kappa B (NF-κB). In a rat lung model of fibrosis (bleomycin-induced) there was an elevation of ET-1 levels *prior to* an increase in collagen content which, along with its localization within developing fibrotic lesions, provides further evidence of a pro-fibrotic role for ET-1 at an early stage in the pathogenesis of bleomycin-induced lung fibrosis (20).

Bosentan, by antagonizing the profibrotic properties of ET-1, prevents initiation of fibrosis (3). Bosentan in cell cultures decreases collagen synthesis, increases collagenase expression, inhibits extracellular matrix deposition (4) and reduces NF-κB expression (5).

Consequently bosentan *in vivo* is a potent anti-fibrotic agent in various animal models of fibrosis (6-11).

Since ET-1 is a central player of fibrosis, the findings with bosentan can be extrapolated to all other antagonists of endothelin receptors. For example, in cell cultures, bosentan and another endothelin receptor antagonist, PD 156707, attenuated fibroblast proliferation induced by ET-1 in human fibroblasts (12), increased matrix metalloprotease-1 (collagenase) production (4), and reduced the ability to contract a collagen matrix (13). Another endothelin receptor antagonist, BQ-123, decreased fibronectin synthesis induced by ET-1 or angiotensin II in rat mesangial cells (14). Another antagonist, PED-3512-PI, increased collagenase activity induced by ET-1 and ET-3 in rat cardiac fibroblasts (15).

In *in vivo* models of fibrosis, the endothelin receptor antagonist FR139317 attenuated the expression of collagen, laminin and TGF-β mRNA in diabetic rat kidney (16). Darusentan decreased the accumulation of collagen in norepinephrine -induced aortic remodeling and fibrosis (17). Other endothelin receptor antagonists decreased cardiac fibrosis in heart failure and hypertension models (18, 19).

Experimental setup for the evaluation of the antifibrotic properties of bosentan and of other endothelin receptor antagonists

Experiments were performed on the mouse embryonic fibroblast cell line Swiss 3T3 (Deutsche Sammlung für Mikroorganismen und Zellen, DSMZ ACC 173). Cells were starved for 24 h in serum-free medium or medium containing 0.5% serum followed by a 24 h incubation with endothelin-1 at a concentration giving approximately 50% or preferably 80% of its maximal efficacy, in presence either of vehicle or of an antagonist at increasing concentrations or an antagonist in combination with Pirfenidone.

Potential cytotoxic effects are excluded by assessing fibroblast proliferation using the MTS reagent (21). Collagen neo-synthesis by fibroblasts is assessed by measuring ^{3}H-proline incorporation (22).

Several endothelin receptor antagonists have been tested according to the above-mentioned experimental method.

Experimental results:

In this cell culture model of early fibrosis using Swiss 3T3 mouse embryonic fibroblasts, the concentration-dependent effect of ET-1 on collagen neo-synthesis was measured, and yielded an EC_{50} (concentration of ET-1 giving 50% of maximal effect) of 0.24 nM. Using a concentration of ET-1 of 1 nM (EC_{80}), the below mentioned endothelin receptor antagonists were analyzed for antagonistic activity on ET-1-induced collagen neo-synthesis. Figure 1 shows representative dose-response curves for a selection of tested compounds. The summary for seven tested endothelin receptor antagonists is presented in table 2.

We conclude that all tested antagonists fully antagonize ET-1-induced collagen neo-synthesis to baseline values, with IC_{50} values ranging from 59 nM to 369 nM.

Table 2

IC_{50} values of different ERAs on ET-1-induced collagen neo-synthesis in 3T3 fibroblasts (n>=2)

Compound	IC_{50} (nM)
Bosentan	214
Compound 1	114
Ambrisentan	79
Darusentan	221
TBC3711	59
Sitaxsentan	369
Avosentan	330

Compound 1 = propyl-sulfamic acid {5-(4-bromo-phenyl)-6-[2-(5-bromo-pyrimidin-2-yloxy)-ethoxy]-pyrimidine-4-yl}-amide

Next, the combination of pirfenidone (Sigma P-2116) and bosentan in antagonizing ET-1-induced collagen neo-synthesis was tested. To this end, fibroblasts were treated with either vehicle, bosentan (1 μM), pirfenidone (1 mM) or a combination of bosentan and pirfenidone for 24 h followed by the determination of collagen neo-synthesis. Figure 2 shows the effects of the different compound combinations in ET-1-induced collagen neo-synthesis.

The results show that 1 μM bosentan alone reverses ET-1-induced collagen synthesis to baseline while pirfenidone alone has a 55 % inhibitory effect on collagen neo-synthesis. Combination of both compounds has an additive effect on collagen neo-synthesis leading to a 33 % drop below the value of baseline synthesis.

Clinical evidence

BUILD 1 study was a multicentric, randomized, double-blind, placebo-controlled, phase II/III study in IPF patients. The aim of this study was to demonstrate that bosentan improves the exercise capacity of patients with IPF as assessed by the 6-minute walk test (6MWT) distance. The secondary objectives of the study were to demonstrate that bosentan delays time to death or treatment failure, improves pulmonary function tests (PFTs), dyspnea and quality of life and is safe and well tolerated in this patient population. Treatment failure was defined either as worsening of PFTs or the occurrence of an acute decompensation of IPF. PFT worsening was defined as 2 out of the following 3 criteria

- Decrease from baseline ≥ 10% in Forced vital capacity (FVC)
- Decrease from baseline ≥ 15% in diffusion capacity for carbon monoxide (DLCO).
- Decrease from baseline ≥ 4% in O2 saturation (blood gas) at rest or increase from baseline ≥ 8 mmHg in alveolar capillary O2 gradient (A-a PO2).

Main inclusion criteria: proven IPF diagnosis < 3 years duration, either via a surgical lung biopsy or when not done according to the ATS/ERS consensus criteria (see above). The main inclusion criteria were the presence of FVC ≥50 % of predicted value and DLCO ≥30% of predicted value.

A total of 158 patients were randomly allocated to treatment with bosentan (n = 74) or placebo (n = 84). Overall, 154 randomized patients received at least one dose of study medication and had at least one valid post baseline value for the primary endpoint (n= 71 on bosentan, n = 83 on placebo). Following a screening period (≤ 4 weeks), eligible patients were randomized to either bosentan or placebo (1:1), started on oral bosentan 62.5 mg b.i.d. or matching placebo, and up-titrated at Week 4 to achieve the target dose (125 mg b.i.d. or matching placebo) for the remainder of the treatment Period unless down-titrated for reasons of tolerability. The planned treatment period 1 was 12 months. Patients were evaluated at regular interval up to End-of-Period 1 (Month 12 months) and up to the End-of-Study i.e. when the last patient has his/her last visit. The 6MWT and pulmonary function tests were evaluated at each visit.

The All-Treated set of patients included 154 randomized patients who had received at least one dose of study medication and had at least one valid post baseline value for the

primary endpoint (n = 71 on bosentan, n = 83 on placebo). The treatment groups were generally well matched with regard to demographics and baseline disease characteristics.

Although bosentan did not show improvement in the primary endpoint of the 6MWT at the End-of-Period 1, BUILD-1 showed a positive and clinically relevant trend for the efficacy of bosentan in prevention of clinical worsening. The most important clinical finding was a trend for a treatment effect on the PFT score defined as either the occurrence of death or treatment failure (worsening of PFTs or acute respiratory decompensation) at the End-of-Period 1, which was a pre-defined secondary endpoint, (22.5% in the bosentan group compared to 36.1%, in the placebo group corresponding to a relative risk ratio of 0.62, p = 0.0784). PFT scoring was mainly driven by the change in FVC and DLCO.

Post hoc subpopulation analyses were undertaken to determine which population would best show a treatment effect on PFT scores. Age, gender, site location, baseline walk tests or pulmonary function tests were not predictive of any particular treatment effect with bosentan. Surprisingly, as can be seen in Table 3, the 99 patients who had a surgical lung biopsy to establish the IPF diagnosis showed a dramatic statistically significant treatment effect with a relative risk ratio of 0.32, (95% confidence interval (CI) 0.14-0.74).

Table 3

Produced by sturlor on 31MAR06 - Data dump of 14DEC05
Ro 47-0203, Protocol: AC-052-320
Table PFTP_EOP1_BIO_T: PFTs scores at end of period 1
Analysis set: All treated - Patients with surgical lung biopsy performed

	Placebo	Bosentan
	N=50	N=49
n	50	49
Worsened	19 (38.0%)	6 (12.2%)
95% confidence limits	24.7%, 52.8%	4.6%, 24.8%
Treatment effect:		
Relative risk		0.32
95% confidence limits		0.14, 0.74
p-value Fisher's exact test		0.0050
n	50	49
Improved	0 (0.0%)	2 (4.1%)
95% confidence limits	0.0%, 7.1%	0.5%, 14.0%
Treatment effect:		
Relative risk		
95% confidence limits		
p-value Fisher's exact test		0.2424

(Page 1/1)

In contrast, the 58 patients who were diagnosed without a surgical lung biopsy (SLB) showed no treatment effect (relative risk ratio of 1.36, 95% CI 0.70-2.65). Whether this observation was simply due to a chance finding could only be determined by comparing the baseline characteristics of those 2 subgroups of patients.

As seen on Table 4 the only obvious difference was that the non-SLB patients were older than the SLB patients. There were no parameters of the lung function tests suggesting that one group had a more advanced disease than the other.

Table 4

	SLB diagnosis		Non SLB diagnosis	
	Placebo N=50	Bosentan N=49	Placebo N=34	Bosentan N=24
Sex male (%)	80	64	67.6	70.8
Age mean (yrs)	62.4	64.1	69	68.8
41-60 years (%)	40.0	22.0	17.6	12.5
61-70 yrs (%)	38	52	35.3	41.7
> 70 yrs (%)	22.0	24.0	47.1	45.8
Weight (kg)	88.5	87	77	80.1
Race (white %)	90	92	94.1	91.7
Location (%US)	64	72	67.6	45.8
Duration IPF symptoms(yrs)	2.4	2.2	2.6	2.7
FVC (%)	67.4	67.1	72.8	65.4
Dlco (%)	41.7	43.7	40.9	40.8
TLC (%)	65.1	64.1	67.7	66.0
RV (%)	59.6	58	64	65.6
FEV1(%)	78.9	78.7	86.6	81.5

Yrs years, % percent of predicted value; TLC total lung capacity; RV residual volume; FEV1 forced expiratory volume in 1 sec

As seen on Table 5 the only obvious difference was that the non-SLB patients were older than the SLB patients. The lung function tests were well balanced between the 2 groups.

Table 5

A	Biopsy diagnosis*		CT diagnosis	
	Placebo N=50	Bosentan N=50	Placebo N=34	Bosentan N=24
Sex male (%)	80	64	67.6	70.8
Age mean (yrs)	62.4	64.1	69	68.8
41-60 years (%)	40.0	22.0	17.6	12.5
61-70 yrs (%)	38	52	35.3	41.7
> 70 yrs (%)	22.0	24.0	47.1	45.8
Weight (kg)	88.5	87	77	80.1
Race (white %)	90	92	94.1	91.7
Location (%US)	64	72	67.6	45.8
Duration IPF symptoms (yrs)	2.5	2.4	2.6	2.7
FVC (%)	67.4	67.1	72.8	65.4
Dlco (%)	41.7	43.7	40.9	40.8
TLC (%)	65.1	64.0	67.7	66.0
RV (%)	59.6	58	64	65.6
FEV_1(%)	78.9	78.7	86.6	81.5

* Safety population for which one bosentan patient did not have a post baseline efficacy assessment

Yrs years, % percent of predicted value; TLC total lung capacity; RV residual volume; FEV1 forced expiratory volume in 1 sec

The only remaining logical explanation was that these 2 groups differed in their HRCT at presentation. Before undertaking a central reading of all available CTs, the following hypothesis was built.

Three possible explanations were tested why patients with SLBs would have had a better treatment effect than those without:

- Patients with surgical lung biopsy had little or no honeycombing
- Patients with surgical lung biopsy had less extensive fibrosis, and therefore more difficult to make a confident CT diagnosis
- Patients with surgical lung biopsy had substantially more ground-glass abnormality than the others

With these in mind, we formulated the following hypotheses:

Extent of honeycombing in IPF is a predictor of non-response to treatment.

Extent of ground-glass abnormality is a predictor of response to treatment

The analyses were run by a single radiologist who was blinded to the group allocation. Each patient CT was scored for honeycomb as well as ground-glass from the 3 zones of each lung namely upper mid and lower zone. Increment for HC and ground-glass was rounded to the upper 5%.

Figure 3 summarizes the radiological findings of the 143 available HRCT scans from the BUILD-1 patients. Irrespective of the need for SLB for establishing the diagnosis of IPF the pre-specified hypothesis was verified that the presence of ground-glass or the absence of honeycomb were strong predictors of a treatment effect with bosentan as well as the predominant distribution of abnormality (sub-pleural vs. diffuse or axial peripheral vs. others).

Then we looked at the scoring of honeycombing (HC) vs. the treatment effect. Figure 4 shows that HC score, irrespective of the need for SLB or not to enter the BUILD 1 study was correlated with the treatment effect (relative risk). The same inverse observation was done for the amount of ground-glass on baseline HRCT. The figure suggests that the maximal treatment effect of bosentan is achieved in patients for whom the HC score is between 0 and 10% of the entire lung fields and/or when ground-glass score is present at patient presentation. The figure also suggests that the maximal treatment effect of bosentan is achieved in patients for whom the HC score is up to 25% of the entire lung fields and/or when ground-glass score is present at patient presentation. This treatment effect may have been obtained also on top of background IPF therapy such as interferon gamma 1b, pirfenidone, imatinib, tumor necrosis factor alpha blocker such as etanercept and N-acetyl cysteine.

In conclusion, the analysis of the BUILD 1 data demonstrates that the dual endothelin receptor antagonist bosentan is mainly effective in the prevention of clinical worsening in IPF patients with early disease with low or no honeycomb on HRCT lung scans.

References:

1. Hocher B, Schwarz A, Fagan KA, Thone-Reineke C, El-Hag K, Kusserow H, et al. Pulmonary fibrosis and chronic lung inflammation in ET-1 transgenic mice. Am J Respir Cell Mol Biol 2000;23(1):19–26.

2. Hocher B, Thone-Reineke C, Rohmeiss P, Schmager F, Slowinski T, Burst V, et al. Endothelin-1 transgenic mice develop glomerulosclerosis, interstitial fibrosis, and renal cysts but not hypertension. J Clin Invest 1997;99(6):1380–9.

3. Clozel M, Salloukh H. Role of endothelin in fibrosis and anti-fibrotic potential of bosentan. Annals of Medicine, 2005; 37: 2-12

4. Shi-wen X, Denton CP, Dashwood MR, Holmes AM, Bou-Gharios G, Pearson JD, et al. Fibroblast matrix gene expression and connective tissue remodeling: role of endothelin-1. J Invest Dermatol 2001;116(3):417–25.

5. Wilson SH, Simari RD, Lerman A. The effect of endothelin-1 on nuclear factor kappa B in macrophages. Biochem Biophys Res Commun 2001;286(5):968–72.

6. Park SH, Saleh D, Giaid A, Michel RP. Increased endothelin-1 in bleomycin-induced pulmonary fibrosis and the effect of an endothelin receptor antagonist. Am J Respir Crit Care Med 1997;156(2 Pt 1):600–8.

7. Mulder P, Richard V, Derumeaux G, Hogie M, Henry JP, Lallemand F, et al. Role of endogenous endothelin in chronic heart failure: effect of long- term treatment with an endothelin antagonist on survival, hemodynamics, and cardiac remodeling. Circulation 1997;96(6):1976–82.

8. Seccia TM, Belloni AS, Kreutz R, Paul M, Nussdorfer GG, Pessina AC, et al. Cardiac fibrosis occurs early and involves endothelin and AT-1 receptors in hypertension due to endogenous angiotensin II. J Am Coll Cardiol 2003;41(4):666–73.

9. Ramires FJA, Sun Y, Mady C, Ramires JAF, Weber KT. Effect of endothelin on myocardial fibrosis in response to chronic administration of angiotensin II or aldosterone. Circulation 1999;100(18):S 2500.

10. Boffa JJ, Tharaux PL, Dussaule JC, Chatziantoniou C. Regression of renal vascular fibrosis by endothelin receptor antagonism. Hypertension 2001;37(2 Part 2):490–6.

11. Rockey DC, Chung JJ. Endothelin antagonism in experimental hepatic fibrosis. Implications for endothelin in the pathogenesis of wound healing. J Clin Invest 1996;98(6):1381–8.

12. Shi-wen X, Denton CP, Holmes A, Dashwood MR, Abraham DJ, Black CM. Endothelins: effect on matrix biosynthesis and proliferation in normal and scleroderma fibroblasts. J Cardiovasc Pharmacol 1998;31(Suppl 1):S360–3.

13. Shi-wen X, et al. Endothelin-1 promotes myofibroblast induction through the ETA receptor via a rac/phosphoinositide 3-kinase/Akt-dependent pathway and is essential for the enhanced contractile phenotype of fibrotic fibroblasts. Mol Biol Cell. 2004 15(6):2707-19.

14. Gomez-Garre D, Ruiz-Ortega M, Ortego M, Largo R, Lopez-Armada MJ, Plaza JJ, et al. Effects and interactions of endothelin-1 and angiotensin II on matrix protein expression and synthesis and mesangial cell growth. Hypertension 1996;27(4):885–92.

15. Guarda E, Katwa LC, Myers PR, Tyagi SC, Weber KT. Effects of endothelins on collagen turnover in cardiac fibroblasts. Cardiovasc Res 1993;27(12):2130–4.

16. Nakamura T, Ebihara I, Fukui M, Tomino Y and Koide H. Effect of a specific endothelin receptor A antagonist on mRNA levels for extracellular matrix components and growth factors in diabetic glomeruli. Diabetes 1995; 44: 895-899.

17. DaoHH, Lemay J, de Champlain J, deBlois D and Moreau P. Norepinephrine-induced aortic hyperplasia and extracellular matrix deposition are endothelin-dependent. J Hypertension 1973; 19: 1965-1973.

18. Hocher B, George I, Rebstock J, Bauch A, Schwarz A, Neumayer HH, et al. Endothelin system-dependent cardiac remodeling in renovascular hypertension. Hypertension 1999;33(3):816–22.

19. Mulder P, Boujedaini H, Richard V, Derumeaux G, Henry JP, Renet S, et al. Selective endothelin-A versus combined endothelin-A/endothelin-B receptor blockade in rat chronic heart failure. Circulation 2000;102(5):491–3.

20. Mutsaers SE, Foster ML, Chambers RC, Laurent GJ, McAnulty RJ. Increasedendothelin-1 and its localization during the development of bleomycin-induced pulmonary fibrosis in rats. Am J Respir Cell Mol Biol. 1998;18(5):611-9.

21. Berridge MV, Tan AS. Characterization of the cellular reduction of 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT): subcellular localization, substrate dependence, and involvement of mitochondrial electron transport in MTT reduction. Arch Biochem Biophys. 1993;303(2):474-82.

22. Zacharia LC, Jackson EK, Gillespie DG, Dubey RK. Catecholamines block 2-hydroxyestradiol-induced antimitogenesis in mesangial cells. *Hypertension* 2002; 39 (4): 854-9.

Claims

1. Use of an endothelin receptor antagonist, or a pharmaceutical composition comprising an endothelin receptor antagonist and either pirfenidone or interferon-gamma, for the preparation of a medicament for the treatment of early stage idiopathic pulmonary fibrosis.
2. Use according to claim 1 wherein the endothelin receptor antagonist is a dual endothelin receptor antagonist or a mixed endothelin receptor antagonist.
3. Use according to claim 1 wherein the endothelin receptor antagonist is a selective endothelin receptor antagonist that binds selectively to the ET_A receptor.
4. Use according to claim 1 wherein the endothelin receptor antagonist is a selective endothelin receptor antagonist that binds selectively to the ET_B receptor.
5. Use according to any one of claims 1 to 4 wherein the endothelin receptor antagonist is selected from table 1.
6. Use according to any one of claims 1 to 5 wherein the endothelin receptor antagonist is selected from darusentan, ambrisentan, atrasentan, sitaxsentan, avosentan, TBC-3711, tezosentan, clazosentan, propyl-sulfamic acid {5-(4-bromo-phenyl)-6-[2-(5-bromo-pyrimidin-2-yloxy)-ethoxy]-pyrimidine-4-yl}-amide and bosentan.
7. Use according to any one of claims 1 to 6 wherein the endothelin receptor antagonist is selected from darusentan, ambrisentan, sitaxsentan, avosentan, TBC-3711, propyl-sulfamic acid {5-(4-bromo-phenyl)-6-[2-(5-bromo-pyrimidin-2-yloxy)-ethoxy]-pyrimidine-4-yl}-amide and bosentan.
8. Use according to any one of claims 1 to 7 wherein the endothelin receptor antagonist is bosentan.
9. Use according to any one of claims 1 to 8 wherein honeycomb on HRCT or CT scans is either absent or minimal.
10. Use according to any one of claims 1 to 9 wherein honeycomb on HRCT or CT scans is present in less than 25% of the overall lung fields.
11. Use according to any one of claims 1 to 10 wherein honeycomb on HRCT or CT scans is present in less than 10% of the overall lung fields.
12. Use according to any one of claims 1 to 11 wherein the ground-glass attenuation could be any percentage between above zero to 80 % of lung fields.

13. Use according to claim 8 wherein bosentan is given to a patient at a daily dosage of 125 mg with or without a lower starting dose.
14. Use according to claim 8 wherein bosentan is given to a patient at a daily dosage of 250 mg with or without a lower starting dose.