

(12) STANDARD PATENT
(19) AUSTRALIAN PATENT OFFICE

(11) Application No. **AU 2012212269 B2**

(54) Title
Aerosol pirfenidone and pyridone analog compounds and uses thereof

(51) International Patent Classification(s)
A01N 43/40 (2006.01) **A61K 31/44** (2006.01)
A61K 9/72 (2006.01)

(21) Application No: **2012212269** (22) Date of Filing: **2012.01.31**

(87) WIPO No: **WO12/106382**

(30) Priority Data

(31) Number	(32) Date	(33) Country
61/584,119	2012.01.06	US
61/438,203	2011.01.31	US
61/559,670	2011.11.14	US
61/508,542	2011.07.15	US

(43) Publication Date: **2012.08.09**

(44) Accepted Journal Date: **2016.05.19**

(71) Applicant(s)
Genoa Pharmaceuticals, Inc.

(72) Inventor(s)
Surber, Mark William

(74) Agent / Attorney
AJ PARK, L 9 Nishi 2 Phillip Law St, Canberra, ACT, 2601

(56) Related Art
WO 2004/058256 A1
WO 2000/016775 A1
GB 1529960 A



(51) International Patent Classification:

A01N 43/40 (2006.01) A61K 31/44 (2006.01)
A61K 9/72 (2006.01)

(21) International Application Number:

PCT/US2012/023406

(22) International Filing Date:

31 January 2012 (31.01.2012)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

61/438,203	31 January 2011 (31.01.2011)	US
61/508,542	15 July 2011 (15.07.2011)	US
61/559,670	14 November 2011 (14.11.2011)	US
61/584,119	6 January 2012 (06.01.2012)	US

(71) Applicant (for all designated States except US): **GENOA PHARMACEUTICALS, INC.** [US/US]; 12636 High Bluff Drive, Suite 400, San Diego, CA 92130 (US).

(72) Inventor; and

(75) Inventor/Applicant (for US only): **SURBER, Mark, William** [US/US]; 4647 Edison Street, San Diego, CA 92117 (US).

(74) Agent: **MUNSON, Peter, R.**; Wilson Sonsini Goodrich & Rosati, 650 Page Mill Road, Palo Alto, CA 94304-1050 (US).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM,

AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))

Published:

— with international search report (Art. 21(3))
— before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))

(54) Title: AEROSOL PIRFENIDONE AND PYRIDONE ANALOG COMPOUNDS AND USES THEREOF

(57) Abstract: Formulations of pirfenidone or pyridone analog compounds for aerosolization and use of such formulations for aerosol administration of pirfenidone or pyridone analog compounds for the prevention or treatment of various fibrotic and inflammatory diseases, including disease associated with the lung, heart, kidney, liver, eye and central nervous system. Pirfenidone or pyridone analog compound formulations and delivery options allow for efficacious local delivery of pirfenidone or pyridone analog compound. Compositions include formulations, kits, and devices. Methods include inhalation procedures, indications and manufacturing processes for production and use of the compositions described.

02 May 2016
2012212269

**AEROSOL PIRFENIDONE AND PYRIDONE ANALOG
COMPOUNDS AND USES THEREOF**

PRIORITY CLAIM

5 This application claims benefit of U.S. Provisional Application No. 61/438,203,
entitled "AEROSOL PIRFENIDONE AND PYRIDONE ANALOG COMPOUNDS AND
USES THEREOF" filed on January 31, 2011; U.S. Provisional Application No. 61/508,542,
entitled "AEROSOL PIRFENIDONE AND PYRIDONE ANALOG COMPOUNDS AND
USES THEREOF" filed on July 15, 2011; U.S. Provisional Application No. 61/559,670,
10 entitled "AEROSOL PIRFENIDONE AND PYRIDONE ANALOG COMPOUNDS AND
USES THEREOF" filed on November 14, 2011; U.S. Provisional Application No.
61/584,119, entitled "AEROSOL PIRFENIDONE AND PYRIDONE ANALOG
COMPOUNDS AND USES THEREOF" filed on January 06 2012; all of which are herein
incorporated by reference in their entirety.

FIELD OF THE INVENTION

15 The present invention relates in its several embodiments to liquid, dry powder and
metered-dose formulations for therapeutic inhaled delivery of pyridone compositions such as
pirfenidone to desired anatomical sites, for treatment and/or prophylaxis of a variety of
20 pulmonary, neurologic, cardiovascular and solid organ disease conditions.

BACKGROUND OF THE INVENTION

25 A number of undesirable pulmonary diseases such as interstitial lung disease (ILD;
and sub-class diseases therein), chronic obstructive pulmonary disease (COPD; and sub-class
diseases therein), asthma, and fibrotic indications of the kidney, heart and eye, the diseases
are initiated from an external challenge. By non-limiting example, these effectors can
include infection, cigarette smoking, environmental exposure, radiation exposure, surgical
procedures and transplant rejection. However, other causes related to genetic disposition and
the effects of aging may also be attributed. Described herein are compositions of pirfenidone
or a pyridone analog compound that are suitable for inhalation delivery to the lungs and/or
30 systemic compartment and methods of using such compositions.

02 May 2016
2012212269**SUMMARY**

In a first aspect, the invention provides a method of prophylaxis and/or treatment of an interstitial lung disease and/or a pulmonary fibrotic disease in a human, the method comprising administration to the lungs of the human of an aqueous pharmaceutical composition comprising pirfenidone, water and one or more additional ingredients selected from co-solvents, tonicity agents, sweeteners, surfactants, wetting agents, chelating agents, anti-oxidants, salts, and buffers, wherein the pH is between pH 4.0 and pH 8.0 and the concentration of pirfenidone in the aqueous pharmaceutical composition is between 0.1 mg/mL and 100 mg/mL.

In another aspect, the invention provides a kit comprising:
a unit dosage form of a pharmaceutical composition, the composition comprising an aqueous solution comprising pirfenidone, water and one or more additional ingredients selected from co-solvents, tonicity agents, sweeteners, surfactants, wetting agents, chelating agents, anti-oxidants, salts, and buffers, wherein the pH is between pH 4.0 and pH 8.0, wherein the unit dosage form is adapted for use in a liquid nebulizer, and wherein the concentration of pirfenidone in the aqueous solution is from 0.1 mg/mL to 60 mg/mL, in a container that is adapted for use in a liquid nebulizer;

when used for nebulized administration of the pharmaceutical composition to the lungs of a human.

In a further aspect, the present invention provides an inhalation system for administration to a human of a pharmaceutical composition, the composition comprising an aqueous solution comprising pirfenidone, water and one or more additional ingredients selected from co-solvents, tonicity agents, sweeteners, surfactants, wetting agents, chelating agents, anti-oxidants, salts, and buffers, wherein the pH is between pH 4.0 and pH 8.0 and the concentration of pirfenidone in the aqueous solution is between 0.1 mg/mL and 100 mg/mL, the system comprising:

(a) 0.5 mL to 6 mL of the aqueous solution of pirfenidone; and

(b) a high efficiency liquid nebulizer;

when used for nebulized administration of the pharmaceutical composition to the lungs of the human.

In a further aspect, the invention provides the use of an aqueous pharmaceutical composition for the manufacture of a medicament for administration to the lungs of a human

02 May 2016
2012212269

for the prophylaxis and/or treatment of an interstitial lung disease and/or a pulmonary fibrotic disease, the aqueous pharmaceutical composition comprising pirfenidone, water and one or more additional ingredients selected from co-solvents, tonicity agents, sweeteners, surfactants, wetting agents, chelating agents, anti-oxidants, salts, and buffers, wherein the pH is between pH 4.0 and pH 8.0 and the concentration of pirfenidone in the aqueous pharmaceutical composition is between 0.1 mg/mL and 100 mg/mL.

The invention is as defined in the claims. However, the description which follows may also refer to additional compositions, methods and other subject matter outside the scope of the present claims. This description is retained for technical information.

Also described herein is a pirfenidone or pyridone analog compound formulation composition for oral pulmonary or intranasal inhalation delivery, comprising formulations for aerosol administration of pirfenidone or pyridone analog compounds for the prevention or treatment of various fibrotic and inflammatory diseases, including disease associated with the lung, heart, kidney, liver, eye and central nervous system.

Also described herein is an aqueous solution for nebulized inhalation administration comprising: water; pirfenidone, or a pyridone analog compound, at a concentration from about 10 mg/mL to about 50 mg/mL; and one or more co-solvents. In another aspect, described herein is an aqueous solution for nebulized inhalation administration comprising: water; pirfenidone, or a pyridone analog compound, at a concentration from about 10 mg/mL to about 50 mg/mL; optionally one or more buffers to maintain the pH between about pH 4.0 to about pH 8.0; and one or more co-solvents. In some embodiments, the pH of the aqueous solution is from about pH 4.0 to about pH 8.0. In some embodiments, the pH of the aqueous solution is from about pH 6.0 to about pH 8.0. In some embodiments, described herein is an aqueous solution for nebulized inhalation administration comprising: water; pirfenidone, or a pyridone analog compound, at a concentration from about 0.1 mg/mL to about 60 mg/mL; and one or more co-solvents, wherein the osmolality of the aqueous solution is from about 50 mOsmol/kg to about 6000 mOsmol/kg. In some embodiments, pirfenidone, or a pyridone analog compound, is at a concentration from about 10 mg/mL to about 60 mg/mL. In some embodiments, pirfenidone, or a pyridone analog compound, is at a concentration from about 10 mg/mL to about 50 mg/mL. In some embodiments, pirfenidone, or a pyridone analog compound, is at a concentration from about 15 mg/mL to about 50 mg/mL. In some embodiments, pirfenidone, or a pyridone analog compound, is at a concentration from about

02 May 2016
2012212269

20 mg/mL to about 50 mg/mL. In some embodiments, pirfenidone, or a pyridone analog compound, is at a concentration from about 25 mg/mL to about 50 mg/mL. In some embodiments, pirfenidone, or a pyridone analog compound, is at a concentration from about 30 mg/mL to about 50 mg/mL. In some embodiments, the osmolality of the aqueous solution is from about 50 mOsmol/kg to about 6000 mOsmol/kg. In some embodiments, the osmolality of the aqueous solution is from about 50 mOsmol/kg to about 5000 mOsmol/kg. In some embodiments, the osmolality of the aqueous solution is from about 100 mOsmol/kg to about 5000 mOsmol/kg, from about 300 mOsmol/kg to about 5000 mOsmol/kg, from about 400 mOsmol/kg to about 5000 mOsmol/kg, from about 600 mOsmol/kg to about 5000 mOsmol/kg, from about 1000 mOsmol/kg to about 5000 mOsmol/kg, or from about 2000 mOsmol/kg to about 5000 mOsmol/kg. In some embodiments, the total concentration of co-solvents is from about 1% to about 40% v/v. In some embodiments, the total concentration of co-solvents is from about 1% to about 30% v/v. In some embodiments, the total concentration of co-solvents is from about 1% to about 25% v/v. In some embodiments, the one or more co-solvents are selected from ethanol, propylene glycol, and glycerol. In some embodiments, the one or more co-solvents are selected from ethanol, and propylene glycol. In some embodiments, the aqueous solution includes both ethanol and propylene glycol. In some embodiments, the solution further comprises one or more additional ingredients selected from surfactants, taste masking agents/sweeteners and salts. In some embodiments, the tastemaking agent/sweetener is saccharin, or salt thereof. In some embodiments, the solution further comprises one or more additional ingredients selected from surfactants and salts. In some embodiments, the surfactant is polysorbate 80 or cetylpyridinium bromide. In some embodiments, the salt is sodium chloride or magnesium chloride. In some embodiments, the surfactant is polysorbate 80 or cetylpyridinium bromide, and the salt is sodium chloride or magnesium chloride. In some embodiments, the aqueous solution includes one more buffers selected from a citrate buffer and a phosphate buffer. In some embodiments, the aqueous solution includes a phosphate buffer. In some embodiments, the aqueous solution includes a citrate buffer. In some embodiments, described herein is from about 0.5 mL to about 6 mL of the aqueous solution described herein.

In some embodiments, the solution further comprises one or more additional ingredients selected from surfactants, buffers and salts. In some embodiments, the surfactant

02 May 2016
2012212269

is polysorbate 80 or cetylpyridinium bromide; the buffer is a citrate buffer or phosphate buffer; and the salt is sodium chloride or magnesium chloride.

In some embodiments, the aqueous solution comprises: water; pirfenidone or pyridone analog compound at a concentration from about 10 mg/mL to about 60 mg/mL; one or more co-solvents, wherein the total amount of the one or more co-solvents is about 1% to about 40% v/v, where the one or more co-solvents are selected from about 1% to about 25% v/v of ethanol, about 1% to about 25% v/v of propylene glycol, and about 1% to about 25% v/v of glycerol; and optionally a phosphate buffer that maintains the pH of the solution from about pH 6.0 to about pH 8.0.

In some embodiments, the aqueous solution comprises: water; pirfenidone or pyridone analog compound at a concentration from about 15 mg/mL to about 50 mg/mL; one or more co-solvents, wherein the total amount of the one or more co-solvents is about 1 to about 30% v/v, where the one or more co-solvents are selected from about 1% to about 10% v/v of ethanol, and about 1% to about 20% v/v of propylene glycol; and optionally a phosphate buffer that maintains the pH of the solution from about pH 6.0 to about pH 8.0; wherein the osmolality of the aqueous solution is from about 400 mOsmol/kg to about 6000 mOsmol/kg.

In some embodiments, the aqueous solution for nebulized inhalation administration described herein comprises: water; pirfenidone or pyridone analog compound at a concentration from about 10 mg/mL to about 50 mg/mL; optionally a phosphate buffer that maintains the pH of the solution from about pH 6.0 to about pH 8.0; one or more co-solvents selected from about 1% to about 25% v/v of ethanol and about 1% to about 25% v/v of propylene glycol, where the total amount of co-solvents is from 1% to 25% v/v. In some embodiments, the aqueous solution for nebulized inhalation administration described herein comprises: water; pirfenidone or pyridone analog compound at a concentration from about 10 mg/mL to about 50 mg/mL; optionally a phosphate buffer that maintains the pH of the solution from about pH 6.0 to about pH 8.0; about 8% v/v of ethanol; and about 16% v/v of propylene glycol. In some embodiments, the aqueous solution for nebulized inhalation administration described herein consists essentially of: water; pirfenidone or pyridone analog compound at a concentration from about 10 mg/mL to about 50 mg/mL; optionally a phosphate buffer that maintains the pH of the solution from about pH 6.0 to about pH 8.0;

02 May 2016
2012212269

one or more co-solvents selected from about 1% to about 25% v/v of ethanol and about 1% to about 25% v/v of propylene glycol, where the total amount of co-solvents is from 1% to 25% v/v. In some embodiments, the aqueous solution for nebulized inhalation administration described herein consists essentially of: water; pirfenidone or pyridone analog compound at a concentration from about 10 mg/mL to about 50 mg/mL; optionally a phosphate buffer that maintains the pH of the solution from about pH 6.0 to about pH 8.0; about 8% v/v of ethanol; and about 16% v/v of propylene glycol. In some embodiments, described herein is from about 0.5 mL to about 6 mL of the aqueous solution described herein.

In some embodiments, described herein is a unit dosage adapted for use in a liquid nebulizer comprising from about 0.5 mL to about 6 mL of an aqueous solution of pirfenidone or a pyridone analog compound, wherein the concentration of pirfenidone or pyridone analog compound in the aqueous solution is from about 0.1 mg/mL to about 60 mg/mL. In some embodiments, the aqueous solution further comprises one or more additional ingredients selected from co-solvents, tonicity agents, sweeteners, surfactants, wetting agents, chelating agents, anti-oxidants, salts, and buffers; and the osmolality of the aqueous solution is from about 50 mOsmol/kg to about 6000 mOsmol/kg. In some embodiments, the aqueous solution further comprises: one or more co-solvents selected from ethanol, propylene glycol, and glycerol; and one or both of a citrate buffer or a phosphate buffer. In some embodiments, the aqueous solution comprises: pirfenidone or pyridone analog compound dissolved in water at a concentration from about 15 mg/mL to about 50 mg/mL; optionally a phosphate buffer that maintains the pH of the solution from about pH 6.0 to about pH 8.0; one or more co-solvents, wherein the total amount of the one or more co-solvents is about 1 to about 30% v/v, where the one or more co-solvents are selected from about 1% to about 10% v/v of ethanol, and about 1% to about 20% v/v of propylene glycol; wherein the osmolality of the aqueous solution is from about 400 mOsmol/kg to about 6000 mOsmol/kg. In some embodiments, the aqueous solution is as described herein.

In some embodiments, described herein is a kit comprising: a unit dosage of an aqueous solution of pirfenidone or pyridone analog as described herein in a container that is adapted for use in a liquid nebulizer.

In some embodiments, provided herein is an aqueous droplet of pirfenidone or pyridone analog compound, wherein the aqueous droplet has a diameter less than about 5.0

02 May 2016
2012212269

5 μm . In some embodiments, the aqueous droplet was produced from a liquid nebulizer and an aqueous solution of pirfenidone or pyridone analog compound. In some embodiments, the aqueous solution of pirfenidone or pyridone analog compound is as described herein. In some embodiments, the aqueous solution has concentration of pirfenidone or pyridone analog compound from about 0.1 mg/mL and about 60 mg/mL and an osmolality from about 50 mOsmol/kg to about 6000 mOsmol/kg. In some embodiments, the aqueous droplet is produced by a nebulizing an aqueous solution of pirfenidone or pyridone analog compound as described herein with a nebulizer. In some embodiments, the nebulizer is a liquid nebulizer. In some embodiments, the nebulizer is a high efficiency liquid nebulizer.

10 In some embodiments, provided herein is an aqueous aerosol comprising a plurality of aqueous droplets of pirfenidone or pyridone analog compound. In some embodiments, described herein is an aqueous aerosol comprising a plurality of aqueous droplets of pirfenidone or pyridone analog compound, wherein the plurality of aqueous droplets have a volumetric mean diameter (VMD), mass median aerodynamic diameter (MMAD), and/or mass median diameter (MMD) of less than about 5.0 μm . In some embodiments, the plurality of aqueous droplets was produced from a liquid nebulizer and an aqueous solution of pirfenidone or pyridone analog compound. In some embodiments, the aqueous solution has concentration of pirfenidone or pyridone analog compound from about 10 mg/mL and about 60 mg/mL and an osmolality from about 50 mOsmol/kg to about 6000 mOsmol/kg. In some embodiments, at least 30% of the aqueous droplets in the aerosol have a diameter less than about 5 μm . In some embodiments, the aqueous aerosol is produced by a nebulizing an aqueous solution of pirfenidone or pyridone analog compound as described herein with a nebulizer. In some embodiments, the nebulizer is a liquid nebulizer. In some embodiments, the nebulizer is a high efficiency liquid nebulizer.

25 In some embodiments, the nebulizer used in any of the methods described herein is a liquid nebulizer. In some embodiments, the nebulizer used in any of the methods described herein is a jet nebulizer, an ultrasonic nebulizer, a pulsating membrane nebulizer, a nebulizer comprising a vibrating mesh or plate with multiple apertures, or a nebulizer comprising a vibration generator and an aqueous chamber. In some embodiments, the nebulizer used in any of the methods described herein is a nebulizer comprising a vibrating mesh or plate with multiple apertures. In some embodiments, the liquid nebulizer: (i) achieves lung deposition

02 May 2016
2012212269

of at least 7% of the pirfenidone or pyridone analog compound administered to the mammal; (ii) provides a Geometric Standard Deviation (GSD) of emitted droplet size distribution of the aqueous solution of about 1.0 μm to about 2.5 μm ; (iii) provides: a) a mass median aerodynamic diameter (MMAD) of droplet size of the aqueous solution emitted with the high efficiency liquid nebulizer of about 1 μm to about 5 μm ; b) a volumetric mean diameter (VMD) of about 1 μm to about 5 μm ; and/or c) a mass median diameter (MMD) of about 1 μm to about 5 μm ; (iv) provides a fine particle fraction (FPF= % \leq 5 microns) of droplets emitted from the liquid nebulizer of at least about 30%; (v) provides an output rate of at least 0.1 mL/min; and/or (vi) provides at least about 25% of the aqueous solution to the mammal.

In some embodiments, the liquid nebulizer is characterized as having at least two, at least three, at least four, at least five, or all six of (i), (ii), (iii), (iv), (v), (vi). In some embodiments, the liquid nebulizer: (i) achieves lung deposition of at least 5%, at least 6%, at least 7%, at least 8%, at least 9%, at least 10%, at least 12%, at least 14%, at least 16%, at least 18%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, or at least 80% of the pirfenidone or pyridone analog compound administered to the mammal. In some embodiments, the liquid nebulizer: (ii) provides a Geometric Standard Deviation (GSD) of emitted droplet size distribution of the aqueous solution of about 1.0 μm to about 2.5 μm , about 1.2 μm to about 2.3 μm , about 1.4 μm to about 2.1 μm , or about 1.5 μm to about 2.0 μm . In some embodiments, the liquid nebulizer: (iii) provides a) a mass median aerodynamic diameter (MMAD) of droplet size of the aqueous solution emitted with the high efficiency liquid nebulizer of about less than 5 μm or about 1 μm to about 5 μm ; b) a volumetric mean diameter (VMD) of about less than 5 μm or about 1 μm to about 5 μm ; and/or c) a mass median diameter (MMD) of about less than 5 μm or about 1 μm to about 5 μm . In some embodiments, the liquid nebulizer: (iv) provides a fine particle fraction (FPF= % \leq 5 microns) of droplets emitted from the liquid nebulizer of at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, or at least about 90%. In some embodiments, the liquid nebulizer: (v) provides an output rate of at least 0.1 mL/min, of at least 0.2 mL/min, of at least 0.3 mL/min, of at least 0.4 mL/min, of at least 0.5 mL/min, of at least 0.6 mL/min, of at least 0.7 mL/min,

02 May 2016
2012212269

of at least 0.8 mL/min, of at least 0.9 mL/min, of at least 1.0 mL/min, or less than about 1.0 mL/min. In some embodiments, the liquid nebulizer: (vi) provides at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, or at least about 95%, of the aqueous solution to the mammal. In some embodiments, the liquid nebulizer provides an respirable delivered dose (RDD) of at least 5%, at least 6%, at least 7%, at least 8%, at least 10%, at least 12%, at least 16%, at least 20%, at least 24%, at least 28%, at least 32%, at least 36%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, or at least 90%.

In some embodiments, described herein is a method for the treatment of lung disease in a mammal comprising: administering to mammal in need thereof an aqueous solution comprising pirfenidone or a pyridone analog compound with a liquid nebulizer. In some embodiments, described herein is a method for the treatment of lung disease in a mammal comprising: administering to mammal in need thereof an aqueous solution comprising pirfenidone or a pyridone analog compound with a liquid nebulizer; wherein the aqueous solution comprises water; pirfenidone, or a pyridone analog compound, at a concentration from about 0.1 mg/mL to about 60 mg/mL; and one or more co-solvents, wherein the osmolality of the aqueous solution is from about 50 mOsmol/kg to about 6000 mOsmol/kg.

In some embodiments, the aqueous solution comprises water; pirfenidone or pyridone analog compound at a concentration from about 10 mg/mL to about 60 mg/mL; one or more co-solvents, wherein the total amount of the one or more co-solvents is about 1% to about 40% v/v, where the one or more co-solvents are selected from about 1% to about 25% v/v of ethanol, about 1% to about 25% v/v of propylene glycol, and about 1% to about 25% v/v of glycerol; and optionally a phosphate buffer that maintains the pH of the solution from about pH 6.0 to about pH 8.0. In some embodiments, the aqueous solution comprises water; pirfenidone or pyridone analog compound at a concentration from about 15 mg/mL to about 50 mg/mL; one or more co-solvents, wherein the total amount of the one or more co-solvents is about 1 to about 30% v/v, where the one or more co-solvents are selected from about 1% to about 10% v/v of ethanol, and about 1% to about 20% v/v of propylene glycol; and optionally a phosphate buffer that maintains the pH of the solution from about pH 6.0 to

02 May 2016
2012212269

about pH 8.0; wherein the osmolality of the aqueous solution is from about 400 mOsmol/kg to about 6000 mOsmol/kg. In some embodiments, the nebulizer is a jet nebulizer, an ultrasonic nebulizer, a pulsating membrane nebulizer, a nebulizer comprising a vibrating mesh or plate with multiple apertures, or a nebulizer comprising a vibration generator and an aqueous chamber. In some embodiments, the liquid nebulizer: (i) achieves lung deposition of at least 7% of the pirfenidone or pyridone analog compound administered to the mammal; (ii) provides a Geometric Standard Deviation (GSD) of emitted droplet size distribution of the aqueous solution of about 1.0 μm to about 2.5 μm ; (iii) provides: a) a mass median aerodynamic diameter (MMAD) of droplet size of the aqueous solution emitted with the high efficiency liquid nebulizer of about 1 μm to about 5 μm ; b) a volumetric mean diameter (VMD) of about 1 μm to about 5 μm ; and/or c) a mass median diameter (MMD) of about 1 μm to about 5 μm ; (iv) provides a fine particle fraction (FPF= $\% \leq 5$ microns) of droplets emitted from the liquid nebulizer of at least about 30%; (v) provides an output rate of at least 0.1 mL/min; and/or (vi) provides at least about 25% of the aqueous solution to the mammal.

In some embodiments, the mammal is a human. In some embodiments, the lung disease is lung fibrosis and the mammal is a human. In some embodiments, the lung disease is idiopathic pulmonary fibrosis and the mammal is a human. In some embodiments, the liquid nebulizer delivers from about 0.1 mg to about 360 mg of pirfenidone or pyridone analog compound to the lungs of the mammal in less than about 20 minutes with mass median diameter (MMAD) particles sizes from about 1 to about 5 micron.

In some embodiments, the lung tissue C_{max} and/or AUC of pirfenidone or pyridone analog compound that is obtained after a single administration of the aqueous solution to the mammal with a liquid nebulizer is about the same or greater than the lung tissue C_{max} and/or AUC of pirfenidone or pyridone analog compound that is obtained after a single dose of orally administered pirfenidone or pyridone analog compound at a dose that is from about 80% to about 120% of the dose administered with the liquid nebulizer; and/or the plasma C_{max} and/or AUC of pirfenidone or pyridone analog compound that is obtained after a single administration of the aqueous solution to the mammal with a liquid nebulizer is at least 10% or greater than the plasma C_{max} and/or AUC of pirfenidone or pyridone analog compound that is obtained after a single dose of orally administered pirfenidone or pyridone analog compound at a dose that is from about 80% to about 120% of the dose administered with the

02 May 2016
2012212269

liquid nebulizer. In some embodiments, the lung tissue Cmax of pirfenidone or pyridone analog compound that is obtained after a single administration of the aqueous solution to the mammal with a liquid nebulizer is greater than the lung tissue Cmax of pirfenidone or pyridone analog compound that is obtained after a single dose of orally administered

5 pirfenidone or pyridone analog compound at a dose that is from about 80% to about 120% of the dose administered with the liquid nebulizer. In some embodiments, the lung tissue AUC of pirfenidone or pyridone analog compound that is obtained after a single administration of the aqueous solution to the mammal with a liquid nebulizer is greater than the lung tissue AUC of pirfenidone or pyridone analog compound that is obtained after a single dose of

10 orally administered pirfenidone or pyridone analog compound at a dose that is from about 80% to about 120% of the dose administered with the liquid nebulizer. In some embodiments, the plasma Cmax of pirfenidone or pyridone analog compound that is obtained after a single administration of the aqueous solution to the mammal with a liquid nebulizer is at least 10% or greater than the plasma Cmax of pirfenidone or pyridone analog compound

15 that is obtained after a single dose of orally administered pirfenidone or pyridone analog compound at a dose that is from about 80% to about 120% of the dose administered with the liquid nebulizer. In some embodiments, the plasma AUC of pirfenidone or pyridone analog compound that is obtained after a single administration of the aqueous solution to the mammal with a liquid nebulizer is at least 10% or greater than the plasma AUC of

20 pirfenidone or pyridone analog compound that is obtained after a single dose of orally administered pirfenidone or pyridone analog compound at a dose that is from about 80% to about 120% of the dose administered with the liquid nebulizer.

In some embodiments, the liquid nebulizer delivers from about 0.1 mg to about 360 mg of pirfenidone or pyridone analog compound to the lungs of the mammal in less than

25 about 20 minutes with mass median diameter (MMAD) particles sizes from about 1 to about 5 micron.

In some embodiments, administration with the liquid nebulizer does not include an initial dose-escalation period.

In some embodiments, described herein is a method of reducing the risk of

30 gastrointestinal (GI) adverse events in the treatment of a human with pirfenidone or pyridone analog compound, comprising: administering to the human in need thereof a nebulized

02 May 2016
2012212269

aqueous solution comprising pirfenidone or a pyridone analog compound with a liquid nebulizer; wherein the aqueous solution comprises water; pirfenidone, or a pyridone analog compound, at a concentration from about 0.1 mg/mL to about 60 mg/mL; and one or more co-solvents, wherein the osmolality of the aqueous solution is from about 50 mOsmol/kg to about 6000 mOsmol/kg. In some embodiments, the aqueous solution comprises water; pirfenidone or pyridone analog compound at a concentration from about 10 mg/mL to about 60 mg/mL; one or more co-solvents, wherein the total amount of the one or more co-solvents is about 1% to about 40% v/v, where the one or more co-solvents are selected from about 1% to about 25% v/v of ethanol, about 1% to about 25% v/v of propylene glycol, and about 1% to about 25% v/v of glycerol; and optionally a phosphate buffer that maintains the pH of the solution from about pH 6.0 to about pH 8.0.

In some embodiments, the aqueous solution comprises water; pirfenidone or pyridone analog compound at a concentration from about 15 mg/mL to about 50 mg/mL; one or more co-solvents, wherein the total amount of the one or more co-solvents is about 1 to about 30% v/v, where the one or more co-solvents are selected from about 1% to about 10% v/v of ethanol, and about 1% to about 20% v/v of propylene glycol; and optionally a phosphate buffer that maintains the pH of the solution from about pH 6.0 to about pH 8.0; wherein the osmolality of the aqueous solution is from about 400 mOsmol/kg to about 6000 mOsmol/kg. In some embodiments, the pirfenidone or pyridone analog is administered to treat lung disease in the human. In some embodiments, lung disease is idiopathic pulmonary fibrosis.

In some embodiments, the liquid nebulizer delivers about 0.1 mg to about 360 mg of pirfenidone or pyridone analog compound to the lungs in less than about 20 minutes with mass median diameter (MMAD) particles sizes from about 1 to about 5 micron.

In some embodiments, administration with the liquid nebulizer does not include an initial dose-escalation period.

In some embodiments, about 0.5 mL to about 6 mL of the aqueous solution is administered to the mammal with a liquid nebulizer, the solution having a concentration of pirfenidone or pyridone analog compound from about 0.1 mg/mL to about 60 mg/mL and the osmolality of the aqueous solution is from about 50 mOsmol/kg to about 5000 mOsmol/kg; and the liquid nebulizer is a nebulizer comprising a vibrating mesh or plate with multiple apertures.

02 May 2016

2012212269

In some embodiments, the liquid nebulizer delivers about 0.1 mg to about 360 mg of pirfenidone or pyridone analog compound to the lungs in less than about 20 minutes with mass median diameter (MMAD) particles sizes from about 1 to about 5 micron. In some embodiments, the aqueous solution has a pH from about 4.0 to about 8.0 and an osmolality from about 400 mOsmol/kg to about 5000 mOsmol/kg.

In some embodiments, described herein is an inhalation system for administration of pirfenidone or pyridone analog compound to the respiratory tract of a human, the system comprising: (a) about 0.5 mL to about 6 mL of an aqueous solution of pirfenidone or pyridone analog compound; and (b) a high efficiency liquid nebulizer. In some embodiments, the aqueous solution is any of the aqueous solutions described herein. In some embodiments, the concentration of pirfenidone or pyridone analog compound in the aqueous solution is from about 0.1 mg/mL and about 60 mg/mL and the osmolality of the aqueous solution is from about 400 mOsmol/kg to about 6000 mOsmol/kg. In some embodiments, the aqueous solution comprises: water; pirfenidone, or a pyridone analog compound, at a concentration from about 10 mg/mL to about 50 mg/mL; optionally a phosphate buffer that maintains the pH of the solution from about pH 6.0 to about pH 8.0; about 1% to about 8% of ethanol; and/or about 2% to about 16% of propylene glycol. In some embodiments, the aqueous solution is as described herein.

In one aspect, described herein is a method of achieving a lung tissue C_{max} of pirfenidone or pyridone analog compound that is at least 1.5 times, at least 2 times, at least 3 times, at least 4 times, at least 5 times, at least 6 times, at least 1.5 times, at least 1.5 times, at least 1.5 times, at least 1.5 times, at least 7 times, at least 8 times, at least 9 times, at least 10 times, at least 1.5-20 times, at least 1.5-15 times, at least 1.5-10 times, at least 1.5-5 times, or at least 1.5-3 times times a C_{max} of up to 801 mg of an orally administered dosage of pirfenidone or pyridone analog compound, the method comprising nebulizing an aqueous solution comprising pirfenidone or pyridone analog compound and administering the nebulized aqueous solution to a human. In some embodiments, described herein is a method of achieving a lung tissue C_{max} of pirfenidone or pyridone analog compound that is at least equivalent to or greater than a C_{max} of up to 801 mg of an orally administered dosage of pirfenidone or pyridone analog compound, the method comprising nebulizing an aqueous

02 May 2016
2012212269

solution comprising pirfenidone or pyridone analog compound and administering the nebulized aqueous solution to a human.

In one aspect, described herein is a method of achieving a lung tissue AUC₀₋₂₄ of pirfenidone or pyridone analog compound that is at least 1.5 times, at least 2 times, at least 3 times, at least 4 times, at least 5 times, at least 6 times, at least 1.5 times, at least 1.5 times, at least 1.5 times, at least 1.5 times, at least 7 times, at least 8 times, at least 9 times, at least 10 times, at least 1.5-20 times, at least 1.5-15 times, at least 1.5-10 times, at least 1.5-5 times, or at least 1.5-3 times times AUC₀₋₂₄ of up to 801 mg of an orally administered dosage of pirfenidone or pyridone analog compound, the method comprising nebulizing an aqueous solution comprising pirfenidone or pyridone analog compound and administering the nebulized aqueous solution to a human. In some embodiments, described herein is a method of achieving a lung tissue AUC₀₋₂₄ of pirfenidone or pyridone analog compound that is at least equivalent to or greater than AUC₀₋₂₄ of up to 801 mg of an orally administered dosage of pirfenidone or pyridone analog compound, the method comprising nebulizing an aqueous solution comprising pirfenidone or pyridone analog compound and administering the nebulized aqueous solution to a human.

In one aspect, described herein is a method of administering pirfenidone or a pyridone analog compound to a human, comprising administering a nebulized aqueous solution containing the pirfenidone or pyridone analog, wherein the lung tissue C_{max} achieved with the nebulized solution is at least 1.5 times, at least 2 times, at least 3 times, at least 4 times, at least 5 times, at least 6 times, at least 1.5 times, at least 1.5 times, at least 1.5 times, at least 1.5 times, at least 7 times, at least 8 times, at least 9 times, at least 10 times, at least 1.5-20 times, at least 1.5-15 times, at least 1.5-10 times, at least 1.5-5 times, or at least 1.5-3 times times the lung tissue C_{max} achieved with an orally administered pirfenidone or pyridone analog compound dosage that is from 80% to 120% of the dose amount of pirfenidone that is administered by nebulization.

In one aspect, described herein is a method of administering pirfenidone or a pyridone analog compound to a human, comprising administering a nebulized aqueous solution containing the pirfenidone or pyridone analog, wherein the lung tissue C_{max} achieved with the nebulized solution is at least 1.5 times, at least 2 times, at least 3 times, at least 4 times, at least 5 times, at least 6 times, at least 1.5 times, at least 1.5 times, at least 1.5 times, at least

02 May 2016
2012212269

1.5 times, at least 7 times, at least 8 times, at least 9 times, at least 10 times, at least 1.5-20 times, at least 1.5-15 times, at least 1.5-10 times, at least 1.5-5 times, or at least 1.5-3 times times the lung tissue C_{max} achieved with an orally administered pirfenidone or pyridone analog compound dosage that is from 80% to 120% of the dosage of pirfenidone or pyridone analog compound in the nebulized aqueous solution of pirfenidone or pyridone analog compound. In some embodiments, described herein is a method of administering pirfenidone or a pyridone analog compound to a human, comprising administering a nebulized aqueous solution containing the pirfenidone or pyridone analog, wherein the lung tissue C_{max} achieved with the nebulized solution is at least equivalent to or greater than the lung tissue C_{max} achieved with an orally administered pirfenidone or pyridone analog compound dosage that is from 80% to 120% of the dosage of pirfenidone or pyridone analog compound in the nebulized aqueous solution of pirfenidone or pyridone analog compound that is administered.

In some embodiments, described herein is a method of administering pirfenidone or a pyridone analog compound to a human, comprising administering a nebulized aqueous solution containing the pirfenidone or pyridone analog, wherein the plasma AUC₀₋₂₄ achieved with the nebulized solution is at least 10% or greater than the plasma AUC₀₋₂₄ achieved with an orally administered pirfenidone or pyridone analog compound dosage that is from 80% to 120% of the dosage of pirfenidone or pyridone analog compound in the nebulized aqueous solution of pirfenidone or pyridone analog compound that is administered.

In one aspect, described herein is a method of administering pirfenidone or a pyridone analog compound to a human, comprising administering a nebulized aqueous solution containing the pirfenidone or pyridone analog, wherein the lung tissue AUC₀₋₂₄ achieved with the nebulized solution is at least 1.5 times, at least 2 times, at least 3 times, at least 4 times, at least 5 times, at least 6 times, at least 1.5 times, at least 1.5 times, at least 1.5 times, at least 1.5 times, at least 7 times, at least 8 times, at least 9 times, at least 10 times, at least 1.5-20 times, at least 1.5-15 times, at least 1.5-10 times, at least 1.5-5 times, or at least 1.5-3 times times the lung tissue AUC₀₋₂₄ achieved with an orally administered pirfenidone or pyridone analog compound dosage that is from 80% to 120% of the dosage of pirfenidone or pyridone analog compound in the nebulized aqueous solution of pirfenidone or pyridone analog compound. In some embodiments, described herein is a method of administering pirfenidone or a pyridone analog compound to a human, comprising administering a nebulized aqueous

02 May 2016

2012212269

solution containing the pirfenidone or pyridone analog, wherein the lung tissue AUC_{0-24} achieved with the nebulized solution is at least 1.5 times the lung tissue AUC_{0-24} achieved with an orally administered pirfenidone or pyridone analog compound dosage that is from 80% to 120% of the dosage of pirfenidone or pyridone analog compound in the nebulized aqueous solution of pirfenidone or pyridone analog compound.

In one aspect, provided herein is a method of improving the pharmacokinetic profile obtained in a human following a single oral dose administration of pirfenidone or pyridone analog. In some embodiments, the human the pirfenidone or pyridone analog is administered to the human to treat lung disease. In some embodiments, the lung disease is lung fibrosis.

In some embodiments, the lung disease is idiopathic pulmonary fibrosis. In some embodiments, the single oral dose comprises up to about 801mg of pirfenidone or pyridone analog compound. In some embodiments, the method of improving the pharmacokinetic profile comprises the step of administering pirfenidone or pyridone analog by inhalation. In some embodiments, the pharmacokinetic profile comprises the lung tissue pharmacokinetic profile. In some embodiments, the pharmacokinetic profile comprises the lung tissue pharmacokinetic profile and/or plasma pharmacokinetic profile. In some embodiments, the pirfenidone or pyridone analog is administered as an aqueous solution with a liquid nebulizer. In some embodiments, the aqueous solution of pirfenidone or pyridone analog is as described herein. In some embodiments, the method of improving the pharmacokinetic profile further comprises a comparison of the pharmacokinetic parameters following inhalation administration to the same parameters obtained following oral administration. In some embodiments, the improvement in pharmacokinetic profile is substantially the same as depicted in Figure 1. In some embodiments, the initial improvement in pharmacokinetic profile is substantially the same as depicted in Figure 1, but the pulmonary half-life is extended providing longer pulmonary residence time.

In some embodiments, described herein is a pharmaceutical composition for pulmonary delivery, comprising a solution of pirfenidone or pyridone analog having a concentration greater than about 34 mcg/mL, having an osmolality greater than about 100 mOsmol/kg, and having a pH greater than about 4.0. In some embodiments, the pirfenidone or pyridone analog concentration is greater than about 1.72 mg/mL. In some embodiments,

02 May 2016
2012212269

the pirfenidone or pyridone analog concentration is greater than about 86 mg/mL. In some
embodiments, the pirfenidone or pyridone analog solution has a permeant ion concentration
from about 30 mM to about 300 mM. In some embodiments, the permeant ion is chloride or
bromide. In some embodiments, the pirfenidone or pyridone analog solution has a pH from
5 about 4.0 to about 8.0. In some embodiments, the pirfenidone or pyridone analog solution
has an osmolality from about 100 mOsmol/kg to about 1000 mOsmol/kg. In some
embodiments, the pirfenidone or pyridone analog solution has an osmolality from about 50
mOsmol/kg to about 5000 mOsmol/kg. In some embodiments, the composition comprises a
taste masking agent. In some embodiments, the taste masking agent is selected from the
10 group consisting of lactose, sucrose, dextrose, saccharin, aspartame, sucralose, ascorbate and
citrate. In some embodiments, the composition comprises a mucolytic agent suitable for
pulmonary delivery. In some embodiments, the composition comprises a second anti-fibrotic
agent suitable for pulmonary delivery. In some embodiments, the composition comprises a
second anti-inflammatory agent suitable for pulmonary delivery.

15 In some embodiments, described herein is a pharmaceutical composition for
pulmonary delivery, comprising a solution of pirfenidone or pyridone analog and a taste
masking agent, wherein the solution has an osmolality greater than about 100 mOsmol/kg,
and a pH greater than about 4.0. In some embodiments, the pirfenidone or pyridone analog
concentration is greater than about 34 mcg/mL. In some embodiments, the pirfenidone or
20 pyridone analog concentration is greater than about 1.72 mg/mL. In some embodiments, the
pirfenidone or pyridone analog concentration is greater than about 86 mg/mL. In some
embodiments, the pirfenidone or pyridone analog solution has a permeant ion concentration
from about 30 mM to about 300 mM. In some embodiments, the permeant ion is chloride or
bromide. In some embodiments, the pirfenidone or pyridone analog solution has a pH from
25 about 4.0 to about 8.0. In some embodiments, the pirfenidone or pyridone analog solution
has an osmolality from about 100 mOsmol/kg to about 1000 mOsmol/kg. In some
embodiments, the pirfenidone or pyridone analog solution has an osmolality from about 50
mOsmol/kg to about 5000 mOsmol/kg. In some embodiments, the composition comprises a
taste masking agent. In some embodiments, the taste masking agent is selected from the
30 group consisting of lactose, sucrose, dextrose, saccharin, aspartame, sucralose, ascorbate and
citrate. In some embodiments, the composition comprises a mucolytic agent suitable for

02 May 2016
2012212269

pulmonary delivery. In some embodiments, the composition comprises a second anti-fibrotic agent suitable for pulmonary delivery. In some embodiments, the composition comprises a second anti-inflammatory agent suitable for pulmonary delivery.

In some embodiments, described herein is a sterile, single-use container comprising
5 from about 0.1 mL to about 20 mL of a solution of pirfenidone or pyridone analog having a concentration greater than about 34 mcg/mL, having an osmolality greater than about 100 mOsmol/kg, and having a pH greater than about 4.0. In some embodiments, the pirfenidone or pyridone analog concentration is greater than about 1.72 mg/mL. In some embodiments, the pirfenidone or pyridone analog concentration is greater than about 86 mg/mL. In some
10 embodiments, the pirfenidone or pyridone analog solution has a permeant ion concentration from about 30 mM to about 300 mM. In some embodiments, the permeant ion is chloride or bromide. In some embodiments, the pirfenidone or pyridone analog solution has a pH from about 4.0 to about 8.0. In some embodiments, the pirfenidone or pyridone analog solution has an osmolality from about 100 mOsmol/kg to about 1000 mOsmol/kg. In some
15 embodiments, the pirfenidone or pyridone analog solution has an osmolality from about 50 mOsmol/kg to about 5000 mOsmol/kg. In some embodiments, the container further comprises a taste masking agent. In some embodiments, the taste masking agent is selected from the group consisting of lactose, sucrose, dextrose, saccharin, aspartame, sucralose, ascorbate and citrate. In some embodiments, the container further comprises a mucolytic
20 agent suitable for pulmonary delivery. In some embodiments, the container further comprises a second anti-fibrotic agent suitable for pulmonary delivery. In some embodiments, the container further comprises a second anti-inflammatory agent suitable for pulmonary delivery.

In one aspect, described herein is a method to treat a pulmonary disease comprising
25 inhaling an aerosol of pirfenidone or pyridone analog solution having a concentration greater than about 34 mcg/mL, having an osmolality greater than about 100 mOsmol/kg, and having a pH greater than about 4.0. In some embodiments, the pirfenidone or pyridone analog concentration is greater than about 1.72 mg/mL. In some embodiments, the pirfenidone or pyridone analog concentration is greater than about 86 mg/mL. In some embodiments, the
30 pirfenidone or pyridone analog solution has a permeant ion concentration from about 30 mM to about 300 mM. In some embodiments, the permeant ion is chloride or bromide. In some

02 May 2016
2012212269

embodiments, the pirfenidone or pyridone analog solution has a pH from about 4.0 to about 8.0. In some embodiments, the pirfenidone or pyridone analog solution has an osmolality from about 100 mOsmol/kg to about 1000 mOsmol/kg. In some embodiments, the pirfenidone or pyridone analog solution has an osmolality from about 50 mOsmol/kg to about 5000 mOsmol/kg. In some embodiments, the pirfenidone or pyridone analog solution has a taste masking agent. In some embodiments, the taste masking agent is selected from the group consisting of lactose, sucrose, dextrose, saccharin, aspartame, sucralose, ascorbate and citrate. In some embodiments, the method further comprises administering a mucolytic agent suitable for pulmonary delivery. In some embodiments, the method further comprises administering a second anti-fibrotic agent suitable for pulmonary delivery. In some embodiments, the method further comprises administering a second anti-inflammatory agent suitable for pulmonary delivery. In some embodiments, the pulmonary disease is interstitial lung disease. In some embodiments, the interstitial lung disease is idiopathic pulmonary fibrosis. In some embodiments, the interstitial lung disease is radiation-therapy-induced pulmonary fibrosis. In some embodiments, the pulmonary disease is chronic obstructive pulmonary disease. In some embodiments, the pulmonary disease is chronic bronchitis. In some embodiments, the pulmonary disease is asthma. In some embodiments, the aerosol comprises particles having a mean aerodynamic diameter from about 1 micron to about 5 microns. In some embodiments, the aerosol has a mean particle size from about 1 microns to about 5 microns volumetric mean diameter and a particle size geometric standard deviation of less than or equal to 3 microns. In some embodiments, the inhaling step delivers a dose of a least 6.8 mcg pirfenidone or pyridone analog. In some embodiments, the inhaling step delivers a dose of a least 340 mcg pirfenidone or pyridone analog. In some embodiments, the inhaling step delivers a dose of a least 740 mcg pirfenidone or pyridone analog. In some embodiments, the inhaling step delivers a dose of a least 1.7 mg pirfenidone or pyridone analog. In some embodiments, the inhaling step delivers a dose of a least 93 mg pirfenidone or pyridone analog. In some embodiments, the inhaling step delivers a dose of a least 463 mg pirfenidone or pyridone analog. In some embodiments, the inhaling step is performed in less than about 20 minutes. In some embodiments, the inhaling step is performed in less than about 10 minutes. In some embodiments, the inhaling step is performed in less than about 7.5 minutes. In some embodiments, the inhaling step is performed in less than about 5

02 May 2016

2012212269

minutes. In some embodiments, the inhaling step is performed in less than about 2.5 minutes. In some embodiments, the inhaling step is performed in less than about 1.5 minutes. In some embodiments, the inhaling step is performed in less than about 30 seconds. In some embodiments, the inhaling step is performed in less than about 5 breaths. In some
5 embodiments, the inhaling step is performed in less than about 3 breaths.

In one aspect, described herein is a method to administer an anti-fibrotic agent to lungs of a patient, comprising: introducing in a nebulizer a pirfenidone or pyridone analog solution having a concentration greater than about 34 mcg/mL, having an osmolality greater than about 100 mOsmol/kg, and having a pH greater than about 4.0. In another aspect,
10 described herein is a method to administer an anti-inflammatory agent to lungs of a patient, comprising: introducing in a nebulizer a pirfenidone or pyridone analog solution having a concentration greater than about 34 mcg/mL, having an osmolality greater than about 100 mOsmol/kg, and having a pH greater than about 4.0. In some embodiments, the pirfenidone or pyridone analog concentration is greater than about 1.72 mg/mL. In some embodiments,
15 the pirfenidone or pyridone analog concentration is greater than about 86 mg/mL. In some embodiments, the pirfenidone or pyridone analog solution has a permeant ion concentration from about 30 mM to about 300 mM. In some embodiments, the permeant ion is chloride or bromide. In some embodiments, the pirfenidone or pyridone analog solution has a pH from about 4.0 to about 8.0. In some embodiments, the pirfenidone or pyridone analog solution
20 has an osmolality from about 100 mOsmol/kg to about 1000 mOsmol/kg. In some embodiments, the pirfenidone or pyridone analog solution has an osmolality from about 50 mOsmol/kg to about 5000 mOsmol/kg. In some embodiments, the pirfenidone or pyridone analog solution has a taste masking agent. In some embodiments, the taste masking agent is selected from the group consisting of lactose, sucrose, dextrose, saccharin, aspartame,
25 sucrulose, ascorbate and citrate. In some embodiments, the method further comprises administering a mucolytic agent suitable for pulmonary delivery. In some embodiments, the mucolytic agent is inhaled separately from the pirfenidone or pyridone analog solution. In some embodiments, the method further comprises administering a second anti-fibrotic agent suitable for pulmonary delivery. In some embodiments, the method further comprises
30 administering a second anti-inflammatory agent suitable for pulmonary delivery.

02 May 2016
2012212269

In one aspect, described herein is a method to treat an extrapulmonary disease target comprising inhaling an aerosol of pirfenidone or pyridone analog solution having a concentration greater than about 34 mcg/mL, having an osmolality greater than about 100 mOsmol/kg, and having a pH greater than about 4.0 for the purpose of absorbing into the pulmonary vasculature and exposing downstream disease targets to delivered pirfenidone or pyridone analog. In some embodiments, the pirfenidone or pyridone analog concentration is greater than about 1.72 mg/mL. In some embodiments, the pirfenidone or pyridone analog concentration is greater than about 86 mg/mL. In some embodiments, the pirfenidone or pyridone analog solution has a permeant ion concentration from about 30 mM to about 300 mM. In some embodiments, the permeant ion is chloride or bromide. In some embodiments, the pirfenidone or pyridone analog solution has a pH from about 4.0 to about 8.0. In some embodiments, the pirfenidone or pyridone analog solution has an osmolality from about 100 mOsmol/kg to about 1000 mOsmol/kg. In some embodiments, the pirfenidone or pyridone analog solution has an osmolality from about 50 mOsmol/kg to about 5000 mOsmol/kg. In some embodiments, the pirfenidone or pyridone analog solution has a taste masking agent. In some embodiments, the taste masking agent is selected from the group consisting of lactose, sucrose, dextrose, saccharin, aspartame, sucralose, ascorbate and citrate. In some embodiments, the method further comprises administering a mucolytic agent suitable for pulmonary delivery. In some embodiments, the mucolytic agent is inhaled separately from the pirfenidone or pyridone analog solution. In some embodiments, the method further comprises administering a second anti-fibrotic agent suitable for pulmonary delivery. In some embodiments, the method further comprises administering a second anti-inflammatory agent suitable for pulmonary delivery. In some embodiments, the extrapulmonary disease target is the heart. In some embodiments, the extrapulmonary disease target is the kidney. In some embodiments, the extrapulmonary disease target is the liver.

In any of the methods described herein using an aerosol or nebulizer to deliver a pirfenidone or pyridone analog compound to the lungs, the aerosol comprises particles having a mean aerodynamic diameter from about 1 micron to about 5 microns. In some embodiments, the aerosol has a mean particle size from about 1 microns to about 5 microns volumetric mean diameter and a particle size geometric standard deviation of less than or equal to 3 microns. In some embodiments, the inhaling step delivers a dose of at least 6.8

02 May 2016
2012212269

mcg pirfenidone or pyridone analog. In some embodiments, the inhaling step delivers a dose of a least 340 mcg pirfenidone or pyridone analog. In some embodiments, the inhaling step delivers a dose of a least 740 mcg pirfenidone or pyridone analog. In some embodiments, the inhaling step delivers a dose of a least 17 mg pirfenidone or pyridone analog. In some
5 embodiments, the inhaling step delivers a dose of a least 93 mg pirfenidone or pyridone analog. In some embodiments, the inhaling step delivers a dose of a least 463 mg pirfenidone or pyridone analog. In some embodiments, the inhaling step is performed in less than about 20 minutes. In some embodiments, the inhaling step is performed in less than about 10 minutes. In some embodiments, the inhaling step is performed in less than about 7.5 minutes.
10 In some embodiments, the inhaling step is performed in less than about 5 minutes. In some embodiments, the inhaling step is performed in less than about 2.5 minutes. In some embodiments, the inhaling step is performed in less than about 1.5 minutes. In some embodiments, the inhaling step is performed in less than about 30 seconds. In some embodiments, the inhaling step is performed in less than about 5 breaths. In some
15 embodiments, the inhaling step is performed in less than about 3 breaths.

In one aspect, described herein is a method to treat a neurologic disease comprising intranasal inhalation of an aerosol of pirfenidone or pyridone analog solution having a concentration greater than about 34 mcg/mL, having an osmolality greater than about 100 mOsmol/kg, and having a pH greater than about 4.0. In some embodiments, the pirfenidone
20 or pyridone analog concentration is greater than about 1.72 mg/mL. In some embodiments, the pirfenidone or pyridone analog concentration is greater than about 86 mg/mL. In some embodiments, the pirfenidone or pyridone analog solution has a permeant ion concentration from about 30 mM to about 300 mM. In some embodiments, the permeant ion is chloride or bromide. In some embodiments, the pirfenidone or pyridone analog solution has a pH from
25 about 4.0 to about 8.0. In some embodiments, the pirfenidone or pyridone analog solution has an osmolality from about 100 mOsmol/kg to about 1000 mOsmol/kg. In some embodiments, the pirfenidone or pyridone analog solution has an osmolality from about 50 mOsmol/kg to about 5000 mOsmol/kg. In some embodiments, the aerosol further comprises a taste masking agent. In some embodiments, the taste masking agent is selected from the
30 group consisting of lactose, sucrose, dextrose, saccharin, aspartame, sucralose, ascorbate and citrate. In some embodiments, the method further comprises administering a mucolytic agent

02 May 2016
2012212269

suitable for intranasal delivery. In some embodiments, the method further comprises administering a second anti-fibrotic agent suitable for intranasal delivery. In some embodiments, the method further comprises administering a second anti-inflammatory agent suitable for intranasal delivery. In some embodiments, the neurologic disease is multiple sclerosis. In some embodiments, the aerosol comprises particles having a mean aerodynamic diameter from about 1 micron to about 20 microns. In some embodiments, the aerosol has a mean particle size from about 1 microns to about 20 microns volumetric mean diameter and a particle size geometric standard deviation of less than or equal to 3 microns. In some embodiments, the inhaling step delivers a dose of a least 6.8 mcg pirfenidone or pyridone analog. In some embodiments, the inhaling step delivers a dose of a least 340 mcg pirfenidone or pyridone analog. In some embodiments, the inhaling step delivers a dose of a least 740 mcg pirfenidone or pyridone analog. In some embodiments, the inhaling step delivers a dose of a least 1.7 mg pirfenidone or pyridone analog. In some embodiments, the inhaling step delivers a dose of a least 93 mg pirfenidone or pyridone analog. In some embodiments, the inhaling step delivers a dose of a least 463 mg pirfenidone or pyridone analog. In some embodiments, the inhaling step is performed in less than about 20 minutes. In some embodiments, the inhaling step is performed in less than about 10 minutes. In some embodiments, the inhaling step is performed in less than about 7.5 minutes. In some embodiments, the inhaling step is performed in less than about 5 minutes. In some embodiments, the inhaling step is performed in less than about 2.5 minutes. In some embodiments, the inhaling step is performed in less than about 1.5 minutes. In some embodiments, the inhaling step is performed in less than about 30 seconds. In some embodiments, the inhaling step is performed in less than about 5 breaths. In some embodiments, the inhaling step is performed in less than about 3 breaths.

In some embodiments, described herein is a method to administer an anti-demyelination agent to nasal cavity of a patient, comprising: introducing in a nebulizer a pirfenidone or pyridone analog solution having a concentration greater than about 34 mcg/mL, having an osmolality greater than about 100 mOsmol/kg, and having a pH greater than about 4.0. In some embodiments, the pirfenidone or pyridone analog concentration is greater than about 1.72 mg/mL. In some embodiments, the pirfenidone or pyridone analog concentration is greater than about 86 mg/mL. In some embodiments, the pirfenidone or

02 May 2016
2012212269

pyridone analog solution has a permeant ion concentration from about 30 mM to about 300 mM. In some embodiments, the permeant ion is chloride or bromide. In some embodiments, the pirfenidone or pyridone analog solution has a pH from about 4.0 to about 8.0. In some embodiments, the pirfenidone or pyridone analog solution has an osmolality from about 100 mOsmol/kg to about 1000 mOsmol/kg. In some embodiments, the pirfenidone or pyridone analog solution has an osmolality from about 50 mOsmol/kg to about 5000 mOsmol/kg. In some embodiments, the solution further comprises a taste masking agent. In some embodiments, the taste masking agent is selected from the group consisting of lactose, sucrose, dextrose, saccharin, aspartame, sucralose, ascorbate and citrate. In some embodiments, the method further comprises administering a mucolytic agent suitable for intranasal delivery. In some embodiments, the mucolytic agent is inhaled separately from the pirfenidone or pyridone analog solution. In some embodiments, the method further comprises administering a second agent suitable for intranasal delivery.

In any of the methods described herein involving introducing in a nebulizer a pirfenidone or pyridone analog solution, the method involves a step of opening a sterile single-use container containing between about 0.5 mL to about 10 mL of a solution of pirfenidone or pyridone analog solution for introduction into a nebulizer.

In any of the methods described herein involving a nebulizer, the aerosol comprises particles having a mean aerodynamic diameter from about 1 micron to about 5 microns. In some embodiments, the aerosol has a mean particle size from about 1 microns to about 5 microns volumetric mean diameter and a particle size geometric standard deviation of less than or equal to 3 microns. In some embodiments, the aerosol comprises particles having a mean aerodynamic diameter from about 1 micron to about 20 microns. In some embodiments, the aerosol has a mean particle size from about 1 microns to about 20 microns volumetric mean diameter and a particle size geometric standard deviation of less than or equal to 3 microns. In some embodiments, the inhaling step delivers a dose of a least 6.8 mcg pirfenidone or pyridone analog. In some embodiments, the inhaling step delivers a dose of a least 340 mcg pirfenidone or pyridone analog. In some embodiments, the inhaling step delivers a dose of a least 740 mcg pirfenidone or pyridone analog. In some embodiments, the inhaling step delivers a dose of a least 1.7 mg pirfenidone or pyridone analog. In some embodiments, the inhaling step delivers a dose of a least 93 mg pirfenidone or pyridone

02 May 2016
2012212269

analog. In some embodiments, the inhaling step delivers a dose of a least 463 mg pirfenidone or pyridone analog. In some embodiments, the inhaling step is performed in less than about 20 minutes. In some embodiments, the inhaling step is performed in less than about 10 minutes. In some embodiments, the inhaling step is performed in less than about 7.5 minutes.

5 In some embodiments, the inhaling step is performed in less than about 5 minutes. In some embodiments, the inhaling step is performed in less than about 2.5 minutes. In some embodiments, the inhaling step is performed in less than about 1.5 minutes. In some embodiments, the inhaling step is performed in less than about 30 seconds. In some embodiments, the inhaling step is performed in less than about 5 breaths. In some
10 embodiments, the inhaling step is performed in less than about 3 breaths. In some embodiments, the inhaling step is performed in one breath.

In one aspect, provided herein is a kit comprising: a pharmaceutical composition comprising a pirfenidone or pyridone analog solution in a sterile container, wherein the pirfenidone or pyridone analog solution has a concentration greater than about 34 mcg/mL,
15 an osmolality greater than about 100 mOsmol/kg, and a pH greater than about 4.0, and a nebulizer adapted to aerosolize the pirfenidone or pyridone analog solution for delivery to the middle to lower respiratory tract through oral inhalation. In some embodiments, the pirfenidone or pyridone analog concentration is greater than about 1.72 mg/mL. In some
20 embodiments, the pirfenidone or pyridone analog concentration is greater than about 86 mg/mL. In some embodiments, the pirfenidone or pyridone analog solution has a permeant ion concentration from about 30 mM to about 300 mM. In some embodiments, the permeant ion is chloride or bromide. In some embodiments, the pirfenidone or pyridone analog solution has a pH from about 4.0 to about 8.0. In some embodiments, the pirfenidone or
25 pyridone analog solution has an osmolality from about 100 mOsmol/kg to about 1000 mOsmol/kg. In some embodiments, the pirfenidone or pyridone analog solution has an osmolality from about 50 mOsmol/kg to about 5000 mOsmol/kg. In some embodiments, the solution further comprises a taste masking agent. In some embodiments, the taste masking agent is selected from the group consisting of lactose, sucrose, dextrose, saccharin, aspartame, sucralose, ascorbate and citrate. In some embodiments, the kit further comprises
30 a mucolytic agent suitable for pulmonary delivery. In some embodiments, the kit further comprises a second anti-fibrotic agent suitable for pulmonary delivery. In some

02 May 2016
2012212269

embodiments, the kit further comprises a second anti-inflammatory agent suitable for pulmonary delivery.

In another aspect, provided herein is a kit comprising: a pharmaceutical composition comprising a pirfenidone or pyridone analog solution in a sterile container, wherein the
5 pirfenidone or pyridone analog solution has a concentration greater than about 34 mcg/mL, an osmolality greater than about 100 mOsmol/kg, and a pH greater than about 4.0, and a nebulizer adapted to aerosolize the pirfenidone or pyridone analog solution for delivery to the nasal cavity through intranasal inhalation.

In some embodiments, the pirfenidone or pyridone analog concentration is greater
10 than about 1.72 mg/mL. In some embodiments, the pirfenidone or pyridone analog concentration is greater than about 86 mg/mL. In some embodiments, the pirfenidone or pyridone analog solution has a permeant ion concentration from about 30 mM to about 300 mM. In some embodiments, the permeant ion is chloride or bromide. In some
15 embodiments, the pirfenidone or pyridone analog solution has a pH from about 4.0 to about 8.0. In some embodiments, the pirfenidone or pyridone analog solution has an osmolality from about 100 mOsmol/kg to about 1000 mOsmol/kg. In some embodiments, the
20 pirfenidone or pyridone analog solution has an osmolality from about 50 mOsmol/kg to about 5000 mOsmol/kg. In some embodiments, the solution further comprises a taste masking agent. In some embodiments, the taste masking agent is selected from the group consisting
of lactose, sucrose, dextrose, saccharin, aspartame, sucralose, ascorbate and citrate. In some
embodiments, the kit further comprises a mucolytic agent suitable for intranasal delivery. In
some embodiments, the kit further comprises a second anti-fibrotic agent suitable for
intranasal delivery. In some embodiments, the kit further comprises a second anti-
inflammatory agent suitable for intranasal delivery.

In one aspect, described herein is a method for treating lung disease, comprising
25 administering pirfenidone or pyridone analog to a middle to lower respiratory tract of a subject having or suspected of having interstitial lung disease through oral inhalation of an aerosol comprising pirfenidone or pyridone analog, wherein the disease is selected from
interstitial lung disease, including idiopathic pulmonary fibrosis and radiation therapy-
30 induced fibrosis; chronic obstructive pulmonary disease; and asthma. In some embodiments, the subject is identified as having interstitial lung disease. In some embodiments, the subject

02 May 2016

2012212269

is identified as having idiopathic pulmonary fibrosis. In some embodiments, the subject is identified as having radiation therapy-induced pulmonary fibrosis. In some embodiments, the subject is identified as having chronic obstructive pulmonary disease. In some embodiments, the subject is identified as having chronic bronchitis. In some embodiments, the subject is identified as having asthma. In some embodiments, the subject is a subject being mechanically ventilated.

A method for treating extrapulmonary disease, comprising administering pirfenidone or pyridone analog to a middle to lower respiratory tract of a subject having or suspected of having extrapulmonary fibrosis, inflammatory and/or toxicity-related diseases through oral inhalation of an aerosol comprising pirfenidone or pyridone analog for purposes of pulmonary vascular absorption and delivery to extrapulmonary diseased tissues, wherein the disease is selected from cardiac fibrosis, kidney fibrosis, hepatic fibrosis, kidney toxicity and heart toxicity. In some embodiments, the subject is identified as having cardiac fibrosis. In some embodiments, the subject is identified as having kidney fibrosis. In some embodiments, the subject is identified as having hepatic fibrosis. In some embodiments, the subject is identified as having kidney toxicity. In some embodiments, the subject is identified as having heart toxicity. In some embodiments, the subject is a subject being mechanically ventilated.

In one aspect, described herein is a method for treating neurologic disease, comprising administering pirfenidone or pyridone analog to the nasal cavity of a subject having or suspected of having neurologic disease through intranasal inhalation of an aerosol comprising pirfenidone or pyridone analog for purposes of nasal vascular absorption and delivery to central nervous system, wherein the disease is multiple sclerosis. In some embodiments, the subject is identified as having multiple sclerosis. In some embodiments, the subject is a subject being mechanically ventilated.

In one aspect, described herein is a pharmaceutical composition for pulmonary delivery, comprising a dry powder containing pirfenidone or pyridone analog having a dosage content greater than about 1%. In some embodiments, the pirfenidone or pyridone analog dose content is greater than about 6.8 mcg. In some embodiments, the pirfenidone or pyridone analog content is greater than about 340 mcg. In some embodiments, the pirfenidone or pyridone analog content is greater than about 17 mg. In some embodiments,

02 May 2016
2012212269

the pirfenidone or pyridone analog content is greater than about 463 mg. In some embodiments, the powder further comprises a blending agent. In some embodiments, the blending agent is selected from the group consisting of lactose.

In one aspect, described herein is a pharmaceutical composition for pulmonary delivery, comprising a dry powder containing pirfenidone or pyridone analog having a dosage content greater than about 1%. In yet another aspect, described herein is a sterile, single-use container comprising from about 0.5 mg to about 100 mg dry powder containing pirfenidone or pyridone analog having a dosage content greater than about 1%. In a further aspect, described is a method to treat a pulmonary disease comprising inhalation of a dry powder aerosol containing pirfenidone or pyridone dosage content greater than about 1%. In some embodiments, the pirfenidone or pyridone analog dose content is greater than about 6.8 mcg. In some embodiments, the pirfenidone or pyridone analog content is greater than about 340 mcg. In some embodiments, the pirfenidone or pyridone analog content is greater than about 17 mg. In some embodiments, the pirfenidone or pyridone analog content is greater than about 463 mg. In some embodiments, the dry powder further comprises a blending agent. In some embodiments, the blending agent is lactose. In some embodiments, the pulmonary disease is interstitial lung disease. In some embodiments, the interstitial lung disease is idiopathic pulmonary fibrosis. In some embodiments, the interstitial lung disease is radiation-therapy-induced pulmonary fibrosis. In some embodiments, the pulmonary disease is chronic obstructive pulmonary disease. In some embodiments, the pulmonary disease is chronic bronchitis. In some embodiments, the pulmonary disease is asthma. In some embodiments, the aerosol comprises particles having a mean aerodynamic diameter from about 1 micron to about 5 microns. In some embodiments, the aerosol has a mean particle size from about 1 microns to about 5 microns volumetric mean diameter and a particle size geometric standard deviation of less than or equal to 3 microns. In some embodiments, the inhaling step delivers a dose of a least 6.8 mcg pirfenidone or pyridone analog. In some embodiments, the inhaling step delivers a dose of a least 340 mcg pirfenidone or pyridone analog. In some embodiments, the inhaling step delivers a dose of a least 740 mcg pirfenidone or pyridone analog. In some embodiments, the inhaling step delivers a dose of a least 1.7 mg pirfenidone or pyridone analog. In some embodiments, the inhaling step delivers a dose of a least 93 mg pirfenidone or pyridone analog. In some embodiments, the inhaling

02 May 2016

2012212269

step delivers a dose of at least 463 mg pirfenidone or pyridone analog. In some embodiments, the inhaling step is performed in less than about 5 breaths. In some embodiments, the inhaling step is performed in less than about 3 breaths. In some embodiments, the inhaling step is performed in less than about 2 breaths. In some embodiments, the inhaling step is performed in one breath.

In one aspect, provided herein is a method to administer an anti-fibrotic agent to lungs of a subject, comprising: introducing in a dry powder inhaler a pirfenidone or pyridone analog dry powder formulation having a dosage content greater than about 1%. In another aspect, provided herein is a method to administer an anti-inflammatory agent to lungs of a subject, comprising: introducing in a dry powder inhaler a pirfenidone or pyridone analog dry powder formulation having a dosage content greater than about 1%. In yet another aspect, provided herein is a method to treat an extrapulmonary disease target comprising inhalation of a dry powder aerosol containing pirfenidone or pyridone dosage content greater than about 1%. In some embodiments, the extrapulmonary disease target is the heart. In some embodiments, the extrapulmonary disease target is the kidney. In some embodiments, the extrapulmonary disease target is the liver. In yet another aspect, provided herein is a method to treat a neurologic disease comprising intranasal inhalation of a dry powder aerosol containing pirfenidone or pyridone dosage content greater than about 1%. In some embodiments, the neurologic disease is multiple sclerosis. In yet another aspect, provided herein is a method to administer an anti-demyelination agent to nasal cavity of a subject, comprising: introducing in a dry powder inhaler a pirfenidone or pyridone analog dry powder formulation having a dosage content greater than about 1%. In some embodiments, the pirfenidone or pyridone analog dose content is greater than about 6.8 mcg. In some embodiments, the pirfenidone or pyridone analog content is greater than about 340 mcg. In some embodiments, the pirfenidone or pyridone analog content is greater than about 17 mg. In some embodiments, the pirfenidone or pyridone analog content is greater than about 463 mg. In some embodiments, the dry powder comprises a blending agent. In some embodiments, the blending agent is lactose. In some embodiments, the aerosol comprises particles having a mean aerodynamic diameter from about 1 micron to about 5 microns. In some embodiments, the aerosol has a mean particle size from about 1 microns to about 5 microns volumetric mean diameter and a particle size geometric standard deviation of less

02 May 2016
2012212269

than or equal to 3 microns. In some embodiments, the aerosol comprises particles having a mean aerodynamic diameter from about 1 micron to about 20 microns. In some embodiments, the aerosol has a mean particle size from about 1 microns to about 20 microns volumetric mean diameter and a particle size geometric standard deviation of less than or equal to 3 microns. In some embodiments, the inhaling step delivers a dose of a least 6.8 mcg pirfenidone or pyridone analog. In some embodiments, the inhaling step delivers a dose of a least 340 mcg pirfenidone or pyridone analog. In some embodiments, the inhaling step delivers a dose of a least 740 mcg pirfenidone or pyridone analog. In some embodiments, the inhaling step delivers a dose of a least 1.7 mg pirfenidone or pyridone analog. In some embodiments, the inhaling step delivers a dose of a least 17 mg pirfenidone or pyridone analog. In some embodiments, the inhaling step delivers a dose of a least 93 mg pirfenidone or pyridone analog. In some embodiments, the inhaling step delivers a dose of a least 463 mg pirfenidone or pyridone analog. In some embodiments, the inhaling step is performed in less than about 5 breaths. In some embodiments, the inhaling step is performed in less than about 3 breaths. In some embodiments, the inhaling step is performed in less than about 2 breaths. In some embodiments, the inhaling step is performed in one breath. In some embodiments, the method further comprises the step of opening a single-use dry powder container holding between about 0.5 mg to about 10 mg dry powder formulation containing pirfenidone or pyridone analog for introduction into a dry powder inhaler.

In one aspect, described herein is a kit comprising: a pharmaceutical composition comprising a dry powder pirfenidone or pyridone analog formulation in a container, wherein the pirfenidone or pyridone analog dosage content is greater than about 1%; and a dry powder inhaler adapted to aerosolize the pirfenidone or pyridone analog dry powder formulation for delivery to the middle to lower respiratory tract through oral inhalation. In another aspect, described herein is a kit comprising: a pharmaceutical composition comprising a dry powder pirfenidone or pyridone analog formulation in a container, wherein the pirfenidone or pyridone analog dosage content is greater than about 1%, and a dry powder inhaler adapted to aerosolize the pirfenidone or pyridone analog dry powder formulation for delivery to the nasal cavity through intranasal inhalation. In some embodiments, the pirfenidone or pyridone analog dose content is greater than about 6.8 mcg. In some embodiments, the pirfenidone or pyridone analog content is greater than about 340 mcg. In some embodiments, the

02 May 2016
2012212269

pirfenidone or pyridone analog content is greater than about 17 mg. In some embodiments, the pirfenidone or pyridone analog content is greater than about 463 mg. In some embodiments, the powder further comprises a blending agent. In some embodiments, the blending agent is lactose.

5 In one aspect, described herein is a method for treating lung disease, comprising administering pirfenidone or pyridone analog to a middle to lower respiratory tract of a subject having or suspected of having interstitial lung disease through oral inhalation of an aerosol comprising pirfenidone or pyridone analog, wherein the disease is selected from interstitial lung disease, including idiopathic pulmonary fibrosis and radiation therapy-
10 induced fibrosis; chronic obstructive pulmonary disease; and asthma. In some embodiments, the subject is identified as having interstitial lung disease. In some embodiments, the subject is identified as having idiopathic pulmonary fibrosis. In some embodiments, the subject is identified as having radiation therapy-induced pulmonary fibrosis. In some embodiments, the subject is identified as having chronic obstructive pulmonary disease. In some embodiments, the subject is identified as having chronic bronchitis. In some embodiments, the subject is identified as having asthma. In some embodiments, the subject is a subject being mechanically ventilated.

In one aspect, described herein is a method for treating extrapulmonary disease, comprising administering pirfenidone or pyridone analog to a middle to lower respiratory
20 tract of a subject having or suspected of having extrapulmonary fibrosis, inflammatory and/or toxicity-related diseases through oral inhalation of an aerosol comprising pirfenidone or pyridone analog for purposes of pulmonary vascular absorption and delivery to extrapulmonary diseased tissues, wherein the disease is selected from cardiac fibrosis, kidney fibrosis, hepatic fibrosis, kidney toxicity and heart toxicity.

25 In some embodiments, the subject is identified as having cardiac fibrosis. In some embodiments, the subject is identified as having kidney fibrosis. In some embodiments, the subject is identified as having hepatic fibrosis. In some embodiments, the subject is identified as having kidney toxicity. In some embodiments, the subject is identified as having heart toxicity. In some embodiments, the subject is a subject being mechanically ventilated.

30 In one aspect, described herein is a method for treating neurologic disease, comprising administering pirfenidone or pyridone analog to the nasal cavity of a subject having or

02 May 2016

2012212269

suspected of having neurologic disease through intranasal inhalation of an aerosol comprising pirfenidone or pyridone analog for purposes of nasal vascular absorption and delivery to central nervous system, wherein the disease is multiple sclerosis. In some embodiments, the subject is identified as having multiple sclerosis. In some embodiments, the subject is a
5 subject being mechanically ventilated.

In one aspect, described herein is a method of administering pirfenidone or pyridone analog to treat a patient with idiopathic pulmonary fibrosis (IPF), wherein the patient avoids abnormal liver function exhibited by a grade 2 or higher abnormality following oral administration in one or more biomarkers of liver function after pirfenidone or pyridone
10 analog administration, comprising administering to said patient pirfenidone or pyridone analog at doses less than 300 mg per day. In some embodiments, "Grade 2 liver function abnormalities" include elevations in alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP), or gamma-glutamyl transferase (GGT) greater than 2.5-times and less than or equal to 5-times the upper limit of normal (ULN). Grade 2 liver
15 function abnormalities also include elevations of bilirubin levels greater than 1.5-times and less than or equal to 3-times the ULN. In some embodiments, the pirfenidone or pyridone analog is delivered to the patient by oral inhalation or intranasal inhalation. In some embodiments, said one or more biomarkers of liver function is selected from the group consisting of alanine transaminase, aspartate transaminase, bilirubin, and alkaline
20 phosphatase. In some embodiments, the method further comprises the step of measuring one or more biomarkers of liver function. In some embodiments, the blood Cmax following administration of pirfenidone or pyridone analog is less than 10 mcg/mL. In some embodiments, the blood Cmax following administration of pirfenidone or pyridone analog is greater than 10 mcg/mL.

In one aspect, described herein is a method of administering pirfenidone or pyridone analog to treat a patient with idiopathic pulmonary fibrosis (IPF), wherein the patient avoids the incidence of photosensitivity reaction observed following oral administration, comprising administering to said patient pirfenidone or pyridone analog at doses less than 360 mg per
25 day. In some embodiments, the pirfenidone or pyridone analog is delivered to the patient by oral inhalation or intranasal inhalation. In some embodiments, the incidence of
30 photosensitivity reaction adverse events is less than about 12%. In some embodiments, the

02 May 2016
2012212269

blood Cmax following administration of pirfenidone or pyridone analog is less than 10 mcg/mL. In some embodiments, the blood Cmax following administration of pirfenidone or pyridone analog is greater than 10 mcg/mL.

5 In one aspect, described herein is a method of administering pirfenidone or pyridone analog to treat a patient with idiopathic pulmonary fibrosis (IPF), wherein the patient avoids the incidence of phototoxicity observed following oral administration, comprising administering to said patient pirfenidone or pyridone analog at doses less than 360 mg per day. In some embodiments, the pirfenidone or pyridone analog is delivered to the patient by oral inhalation or intranasal inhalation. In some embodiments, the incidence of
10 photosensitivity reaction adverse events is less than about 12%. In some embodiments, the blood Cmax following administration of pirfenidone or pyridone analog is less than 10 mcg/mL. In some embodiments, the blood Cmax following administration of pirfenidone or pyridone analog is greater than 10 mcg/mL.

15 In one aspect, described herein is a method of administering pirfenidone or pyridone analog to treat a patient with idiopathic pulmonary fibrosis (IPF), wherein the patient avoids the incidence of gastrointestinal adverse events observed following oral administration, by delivering pirfenidone or pyridone analog directly to the lung by oral inhalation or intranasal inhalation. In some embodiments, gastrointestinal adverse events observed following oral administration of pirfenidone or pyridone analog include, but are not limited to any one or
20 more of the following: dyspepsia, nausea, diarrhea, gastroesophageal reflux disease (GERD) and vomiting. In some embodiments, less than 360 mg per day of pirfenidone or pyridone analog is delivered to the patient by inhalation. In some embodiments, less than 1000mg, less than 900mg, less 600 mg, or less than 300 mg per day of pirfenidone or pyridone analog is delivered to the patient by inhalation. In some embodiments, less than 300 mg per day of
25 pirfenidone or pyridone analog is delivered per dose to the patient by inhalation. In some embodiments, pirfenidone or pyridone analog is delivered by inhalation once per day, twice per day, three time a day, or four time a day.

In some embodiments, up to about 360 mg of pirfenidone or pyridone analog is delivered to the patient by inhalation per dose. In some embodiments, about 1mg to about
30 360mg, about 10mg to about 360mg, about 20mg to about 360mg, about 30mg to about 360mg, about 40mg to about 360mg, about 50mg to about 360mg, about 60mg to about

02 May 2016

2012212269

70mg, about 80mg to about 360mg, about 90mg to about 360mg, about 100mg to about 360mg, about 120mg to about 360mg, about 140mg to about 360mg, about 160mg to about 360mg, about 180mg to about 360mg, or about 200mg to about 360mg, of pirfenidone or pyridone analog is delivered to the patient by inhalation per dose. In some embodiments, 5 pirfenidone or pyridone analog is delivered by inhalation once per day, twice per day, three time a day, or four time a day.

In one aspect, described herein is a pharmaceutical composition comprising a therapeutically effective amount of an inhaled agent, wherein the agent is pirfenidone or pyridone analog, wherein the agent is in a particle less than 5 microns in mass mean 10 aerodynamic diameter or less than 10 microns volumetric mean diameter wherein the composition, upon inhalation, delivers a dose to the lung greater than 1 mcg pirfenidone or pyridone analog compound per gram of adult human lung tissue.

In one aspect, described herein is a pharmaceutical composition for aerosol delivery to the lung, comprising a solution of pirfenidone or pyridone analog containing a divalent 15 cation. In some embodiments, the divalent cation is selected from the group consisting of calcium, iron, magnesium, and beryllium. In some embodiments, the ratio of pirfenidone or pyridone analog to divalent cation is within the molar range of 1 to about 0.1 to 10, in unit increments of about 0.01. By example, 1 to about 10, 1 to about 9, 1 to about 8, 1 to about 7, 1 to about 6, 1 to about 5, 1 to about 4, 1 to about 3, 1 to about 2, 1 to about 1.5, 1 to about 1, 20 1 to about 0.75, 1 to about 0.5, 1 to about 0.25, and 1 to about 0.1. In some embodiments, the active pharmaceutical ingredient is pirfenidone or pyridone analog concentration is between 0.1 mg/mL and 50 mg/mL in unit increments of about 0.01 mg/mL composition. By example, about 0.1 mg/mL, about 0.5 mg/mL, about 1 mg/mL, about 2 mg/mL, about 3 mg/mL, about 4 mg/mL, about 5 mg/mL, about 6 mg/mL, about 7 mg/mL, about 8 mg/mL, 25 about 9 mg/mL, about 10 mg/mL, about 15 mg/mL, about 20 mg/mL, about 25 mg/mL, about 30 mg/mL, about 30 mg/mL, about 35 mg/mL, about 40 mg/mL, about 45 mg/mL, about 50 mg/mL, about 55 mg/mL, and about 60 mg/mL. In some embodiments, the active pharmaceutical ingredient is not a salt of pirfenidone or pyridone analog. In some embodiments, the composition is a stable, water-soluble formulation. In some embodiments, 30 the osmolality is greater than about 50 mOsmol/kg composition in unit increments of about 1 mOsmol/kg. By example, greater than about 50 mOsmol/kg, about 100 mOsmol/kg, about

02 May 2016
2012212269

150 mOsmol/kg, about 200 mOsmol/kg, about 250 mOsmol/kg, about 300 mOsmol/kg, about 350 mOsmol/kg, about 400 mOsmol/kg, about 450 mOsmol/kg, about 500 mOsmol/kg, about 550 mOsmol/kg, about 600 mOsmol/kg, about 650 mOsmol/kg, about 700 mOsmol/kg, about 750 mOsmol/kg, about 800 mOsmol/kg, about 850 mOsmol/kg, about 900 mOsmol/kg, about 950 mOsmol/kg, about 1000 mOsmol/kg, greater than about 1500 mOsmol/kg, about 2000 mOsmol/kg, about 2500 mOsmol/kg, greater than about 3000 mOsmol/kg, about 3500 mOsmol/kg, about 4000 mOsmol/kg, greater than about 4500 mOsmol/kg, about 5000 mOsmol/kg, about 5500 mOsmol/kg, about 6000 mOsmol/kg, or greater than about 6000 mOsmol/kg. In some embodiments, the pH is greater than about 3.0 in pH unit increments of about 0.1. By example, a pH of about 3, a pH of about 3.5, a pH of about 4, a pH of about 4.5, a pH of about 5, a pH of about 5.5, a pH of about 6, a pH of about 6.5, a pH of about 7, a pH of about 7.5, a pH of about 8, a pH of about 8.5, a pH of about 9, a pH of about 9.5, a pH of about 10 a pH of about 10.5, and a pH of about 11. In some embodiments, the pH is balanced by the inclusion of an organic buffer selected from the group consisting of citric acid, citrate, malic acid, malate, pyridine, formic acid, formate, piperazine, succinic acid, succinate, histidine, maleate, bis-tris, pyrophosphate, phosphoric acid, phosphate, PIPES, ACES, MES, cacodylic acid, carbonic acid, carbonate, ADA (N-(2-Acetamido)-2-iminodiacetic acid). In some embodiments, the pirfenidone or pyridone analog solution contains a permeant ion concentration. In some embodiments, the permeant ion is selected from the group consisting of bromine, chloride, and lithium. In some embodiments, the permeant ion concentration is from about 30 mM to about 300 mM in about 0.1 mM increments. By example, about 30 mM, about 40 mM, about 50 mM, about 60 mM, about 70 mM, about 80 mM, about 90 mM, about 100 mm, about 150 mM, about 200 mM, about 250 mM, and about 300 mM. In some embodiments, the composition further comprises a taste masking agent. In some embodiments, the taste masking agent is selected from the group consisting of lactose, sucrose, dextrose, saccharin, aspartame, sucralose, ascorbate, multivalent cation and citrate. In some embodiments, the taste masking agent concentration is from 0.01 mM to about 50 mM in about 0.01 mM increments. By examples, about 0.01 mM, about 0.05 mM, about 0.1 mM, about 0.2 mM, about 0.3 mM, about 0.4 mM, about 0.5 mM, about 0.6 mM, about 0.7 mM, about 0.8 mM, about 0.9 mM, about 1 mM, about 2 mM, about 3 mM, about 4 mM, about 5 mM, about 6 mM, about 7 mM, about 8 mM, about 9 mM,

02 May 2016
2012212269

about 10 mM, about 15 mM, about 20 mM, about 25 mM, about 30 mM, about 35 mM, about 40 mM, about 45 mM, and about 50 mM.

In some embodiments, the formulations described herein are filled into a primary package. In some embodiments, primary packaging material is taken from the group consisting of glass or plastic, wherein plastic materials may be selected from the group consisting of low-density polyethylene (LDPE), high-density polypropylene (HDPP), or high-density polyethylene (HDPE). In some embodiments, the primary packaging consists of a vial, syringe or ampoule. In some embodiments, the composition is protected from light.

In some embodiments, the compositions described herein are formulated under or to result in conditions of reduced oxygen. In some embodiments, oxygen is reduced by sparging the formulation diluent prior to addition of the active pharmaceutical ingredient. Sparging gases may be selected from the group consisting of carbon dioxide, argon or nitrogen. In some embodiments, oxygen is reduced by sparging the formulation diluent after addition of the active pharmaceutical ingredient. Sparging gases may be selected from the group consisting of carbon dioxide, argon or nitrogen. In some embodiments, oxygen exposure is reduced by replacing the ambient gas headspace of the formulation container with an inert gas. Inert gases may be selected from the group consisting of argon or nitrogen.

In some embodiments, oxygen exposure is reduced by replacing the ambient gas headspace of the primary packaging container with an inert gas. Inert gases may be selected from the group consisting of argon or nitrogen.

In some embodiments, oxygen exposure is reduced by inserting the primary packaging into a gas-impermeable secondary packaging container.

In some embodiments, oxygen exposure is reduced by replacing the ambient gas headspace of the secondary packaging with an inert gas. Inert gases may be selected from the group consisting of argon or nitrogen.

In some embodiments, the aerosol for delivery to the lungs of a mammal described herein contains a fine particle fraction between 10 and 100% with increment units of 1%. By example, about 10%, about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, and about 100%. In some embodiments, the fine particle dose is between about 0.1 mg to about 360 mgs prifenidone or pyridone analog, in

02 May 2016
2012212269

0.1 mg increments. By example, about 0.1 mg, about 0.5 mg, about 1 mg, about 2 mg, about 3 mg, about 4 mg, about 5 mg, about 6 mg, about 7 mg, about 8 mg, about 9 mg, about 10 mg, about 11 mg, about 12 mg, about 13 mg, about 14 mg, about 15 mg, about 16 mg, about 17 mg, about 18 mg, about 19 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, about 50 mg, about 60 mg, about 70 mg, about 80 mg, about 90 mg, about 100 mg, about 150 mg, about 200 mg, about 220 mg, about 240 mg, about 260 mg, about 280 mg, about 300 mg, about 320 mg, about 340 mg, or about 360 mg.

In some embodiments, the compositions further comprise a mucolytic agent suitable for pulmonary delivery. In some embodiments, the compositions further comprise a second anti-fibrotic agent suitable for pulmonary delivery. In some embodiments, the compositions further comprise a second anti-inflammatory agent suitable for pulmonary delivery.

These and other aspects of the invention will be evident upon reference to the following detailed description. All of the U.S. patents, U.S. patent application publications, U.S. patent applications, foreign patents, foreign patent applications and non-patent publications referred to in this specification, are incorporated herein by reference in their entirety, as if each was incorporated individually. Aspects of the invention can be modified, if necessary, to employ concepts of the various patents, applications and publications to provide yet further embodiments of the invention.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1 shows a modeled nebulized aerosol administration of pirfenidone and oral administration of pirfenidone to a human subject.

DETAILED DESCRIPTION

A number of undesirable pulmonary diseases such as interstitial lung disease (ILD; and sub-class diseases therein), chronic obstructive pulmonary disease (COPD; and sub-class diseases therein), asthma, and fibrotic indications of the lungs, kidney, heart and eye, are initiated from an external challenge. By non-limiting example, these effectors can include infection, cigarette smoking, environmental exposure, radiation exposure, surgical procedures and transplant rejection. However, other causes related to genetic disposition and the effects of aging may also be attributed.

02 May 2016
2012212269

5 In epithelium, scarring serves a valuable healing role following injury. However, epithelium tissue may become progressively scarred following more chronic and or repeated injuries resulting in abnormal function. In the case of idiopathic pulmonary fibrosis (IPF; and other subclasses of ILD), if a sufficient proportion of the lung becomes scarred respiratory failure can occur. In any case, progressive scarring may result from a recurrent series of insults to different regions of the organ or a failure to halt the repair process after the injury has healed. In such cases the scarring process becomes uncontrolled and deregulated. In some forms of fibrosing disease scarring remains localized to a limited region, but in others it can affect a more diffuse and extensive area resulting in direct or associated organ failure.

10 In neurologic disease, inflammatory destruction of myelin (demyelination) is considered the initial event in diseases such as multiple sclerosis. Demyelination causes scarring and hardening (sclerosis) of nerve tissue in the spinal cord, brain, and optic nerves. Demyelination slows conduction of nerve impulses, which results in weakness, numbness, pain, and vision loss.

15 In epithelial injury, epithelial cells are triggered to release several pro-fibrotic mediators, including the potent fibroblast growth factors transforming growth factor-beta (TGF-beta), tumor necrosis factor (TNF), endothelin, cytokines, metalloproteinases and the coagulation mediator tissue factor. Importantly, the triggered epithelial cell becomes vulnerable to apoptosis, and together with an apparent inability to restore the epithelial cell layer are the most fundamental abnormalities in fibrotic disease. In the case of demyelination, abnormal TNF expression or activity is considered a primary cause of multiple sclerosis and other neurologic disorders, such as rheumatoid disease.

25 In conditions such as pulmonary, kidney, cardiac and ocular fibrosis, multiple sclerosis and rheumatoid disease, physiological responses characterized by control of pro-inflammatory and pro-fibrotic factors with pyridone analogs, such as pirfenidone may be beneficial to attenuate and/or reverse fibrosis and demyelination. Therapeutic strategies exploiting such pyridone analog and/or pirfenidone effects in these and other indications are contemplated herein.

30 TNF-alpha is expressed in asthmatic airways and may play a key role in amplifying asthmatic inflammation through the activation of NF-kappaB, AP-1 and other transcription factors. IgE receptor activation induces TNF-alpha release from human lung tissue and

02 May 2016
2012212269

upregulates eosinophil TNF mRNA levels. TNF-alpha causes transient bronchial hyper-responsiveness likely through a muscarinic receptor expression-mediated response.

TNF-alpha is also believed to play a central role in the pathophysiology of COPD. It is produced by alveolar macrophages, neutrophils, T cells, mast cells and epithelial cells following contact with different pollutants including cigarette smoke. TNF-alpha has been shown in animal models to induce pathological features associated with COPD, such as an inflammatory cell infiltrate into the lungs, pulmonary fibrosis and emphysema. Intriguingly, TNF-alpha levels in sputum increase significantly during acute exacerbations of COPD.

The mechanism of action for pyridone analogs, such as pirfenidone is believed to be both anti-inflammatory and anti-fibrotic. Pirfenidone inhibits synthesis and release of pro-inflammatory cytokines and reduces the accumulation of inflammatory cells in response to various stimuli. Pirfenidone also attenuates fibroblast proliferation, production of fibrosis associated proteins and cytokines, and the increased biosynthesis and accumulation of extracellular matrix in response to cytokine growth factors such as TGF-beta and platelet-derived growth factor (PDGF).

In *in vitro* cell-based assays, pirfenidone suppressed the proliferation of fibroblasts; inhibited lipopolysaccharide (LPS)-stimulated release of PDGF, tumor necrosis factor alpha (TNF-alpha), and TGF- beta1; and inhibited collagen synthesis. Depending on the assay conditions, these *in vitro* activities were evident at pirfenidone concentrations of about 30 microM to about 10 mM (about 5.5 mcg/mL to about 1.85 mg/mL). Given that the oral Cmax of pirfenidone in IPF patients is about 42 microM in the recommended fed-state to about 84 microM in the fasting-state (or about 7.9 mcg/mL to about 15.7 mcg/mL, respectively), these same activities may be promoted *in vivo*, albeit in the lower range of observed efficacy.

Oral administration of pirfenidone to LPS-challenged mice resulted in dose-dependent decreased mortality, reduced serum levels of the pro-inflammatory cytokines TNF-alpha, interleukin (IL-12) and interferon gamma, and increased serum levels of the anti-inflammatory cytokine, IL-10. Pirfenidone treatment also prevented LPS-related hemorrhagic necrosis and apoptosis in the liver, and suppressed increases in TGF-beta.

In vitro studies suggest that pirfenidone may also suppress fibrogenesis through selective inhibition of p38 mitogen-activated protein kinase (MAPK). These observations

02 May 2016

2012212269

have been associated with an attenuation of TGF-beta-induced collagen synthesis. The parallel observation that silencing p38 may also restore sensitivity to corticosteroids in COPD is also promising for this and other disease populations. Unfortunately, compounds that inhibit p38 MAPK have also proven toxic and have been withdrawn from the clinical setting. These compounds have each employed oral administration.

In rat, hamster, and mouse models of bleomycin-induced lung fibrosis, prophylactic administration of pirfenidone reduced pulmonary fibrosis assessed by both histopathological analysis and quantitative determination of collagen content. Pirfenidone treatment also reduced pulmonary edema and pulmonary levels of TGF-beta, basic fibroblast growth factor (bFGF), and various pro-inflammatory cytokines.

In rat, pirfenidone decreased collagen production and deposition in hepatic fibrosis, reversed cardiac and renal fibrosis, and attenuated the increase in diastolic stiffness of diabetic hearts from streptozotocin-treated animals without normalizing cardiac contractility or renal function. In DOCA-salt hypertensive rats, pirfenidone also reversed and prevented cardiac remodeling, and reversed and prevented increased cardiac stiffness without reversing the increased vascular responses to noradrenaline.

Human studies have shown some clinical anti-inflammatory and anti-fibrotic benefit of oral pirfenidone. Phototoxicity, gastrointestinal disorders and abnormal liver function test values may result in human populations following oral administration of pirfenidone. As a consequence patient dosing must be closely monitored. In Phase 3 clinical studies with orally administered pirfenidone, initial dose escalation was required to establish gastrointestinal tolerance. However, dose levels are also limited during or following escalation due to occurrence of nausea, rash, dyspepsia, dizziness, vomiting, photosensitivity reaction, anorexia, and elevated AST and ALT serum transaminases. In some cases, oral administration of pirfenidone may result in dose de-escalation or discontinuation of pirfenidone administration.

In addition to required pirfenidone dose escalation to establish gastrointestinal tolerance, dose de-escalation and the use of food has been employed to enable oral administration to individuals unable to achieve tolerance and would otherwise be removed from therapy, for example, dose de-escalation of up to and greater than 50%. Further, clinical studies utilizing the use of food to enable dose tolerability may also be attempted. In

02 May 2016
2012212269

both cases, the plasma C_{max} is reduced dose-proportionately. More specifically, the fed-state results in about a 50% reduction in C_{max}, about a seven-fold increase in T_{max} and a reduction in overall exposure of 10-15%. Both fed and fasted state resulted in a plasma half-life of about 2.5 hours. While this approach may reduce gastrointestinal-related adverse events, the lack of clinically-significant efficacy in recent orally-administered clinical studies may have been influenced by these approaches.

Based upon clinical observations and adverse events as well as observed toxicities, oral pirfenidone therapy is limited to doses up to about 1800 mg/day to about 2400 mg/day (from 600 mg TID or 801 mg TID, respectively). Thus, while pirfenidone exhibits a wide range of non-human efficacy, human adverse events and toxicities have limited oral dosing to the lower end of this range.

Regulatory risk-benefit analysis between observed efficacy and associated adverse events of orally administered pirfenidone has led to concerns that these doses do not provide sufficient efficacy to warrant the safety risk; even in a terminal population of unmet clinical need. Provided herein in certain embodiments, is a method of administering an equivalent or increased pirfenidone or pyridone analog dose directly to the disease site (e.g., inhalation delivery to the lung) would provide equivalent or improved efficacy over oral routes. In certain embodiments, these doses require less administered drug. In certain embodiments, this approach of administering pirfenidone by inhalation may also benefit from reduced systemic exposure and an increased safety margin when compared to oral administration of pirfenidone. Described herein are compositions of pirfenidone or a pyridone analog compound that are suitable for delivery to a mammal by inhalation and methods of using such compositions.

It is unclear from the existing data whether pirfenidone anti-inflammatory or anti-fibrotic mechanism or mechanisms of action are driven by C_{max} or exposure (area under the curve, AUC). In some embodiments, low to moderately-observed clinical efficacy may be associated with pirfenidone plasma levels about or greater than 5 mcg/mL, exposures (AUC_{0-infinity}) about or greater than 50 mg·hr/L, and/or a plasma elimination rate of about 2.5 hours.

In some embodiments, intravenous or oral administration of pirfenidone may result in lung epithelial lining fluid (ELF) levels comparable to that observed in plasma, and thus, in some embodiments, clinically-measured plasma C_{max} of about or greater than 5 mcg/mL are

02 May 2016

2012212269

directly associated with low to moderately-observed clinical pulmonary efficacy. In some
embodiments, plasma levels of pirfenidone resulting from oral administration are associated
with lower efficacy, and thus in some embodiments the resultant ELF and lung tissue levels
are also associated with lower efficacy. In other embodiments, intravenous or oral
5 administration of pirfenidone may result in lung epithelial lining fluid (ELF) levels less than
that observed as efficacious from the plasma. In some embodiments, ELF levels
corresponding with oral or intravenous-delivered, plasma-observed efficacious levels may be
0.1 mcg/mL to about 5 mcg/mL. In some embodiments, ELF levels corresponding with
plasma-observed efficacious levels may be 0.1 mcg/mL to about 1 mcg/mL. In some
10 embodiments, ELF levels corresponding with oral or intravenous-delivered, plasma-observed
efficacious levels may be 0.5 mcg/mL to about 5 mcg/mL. In some embodiments, ELF levels
corresponding with oral or intravenous-delivered, plasma-observed efficacious levels may be
0.3 mcg/mL to about 3 mcg/mL. In some embodiments, direct administration of pirfenidone
to the lung, results in delivery of about or greater than 5 mcg pirfenidone to one mL ELF, and
15 may result in equivalent pulmonary efficacy without elevated systemic levels associated with
adverse events and toxicities observed with administration. By non-limiting example, this
may be accomplished by oral or intranasal inhaled delivery of aerosolized pirfenidone or
pyridone analog to the lung providing about or greater than 0.1 mcg/mL, for example greater
than about 0.2 mcg/mL, 0.4 mcg/mL, 0.6 mcg/mL, 0.8 mcg/mL, 1.0 mcg/mL, 2 mcg/mL, 3
20 mcg/mL, 4 mcg/mL, 5 mcg/mL, 6 mcg/mL, 7 mcg/mL, 8 mcg/mL, 9 mcg/mL, or greater than
10 mcg/mL of pirfenidone or pyridone analog to the ELF. Once in the ELF, pirfenidone or
pyridone analog will in some embodiments penetrate lung tissue resulting in between about
0.004 mcg and 0.7 mcg pirfenidone or pyridone analog to one gram lung tissue (about 0.1
mcg/mL in about 25 mL ELF to about 5 mcg/mL in about 75 mL ELF, about 600 grams adult
25 human lung tissue weight).

In some embodiments, pirfenidone may readily equilibrate between the plasma and
lung, and/or other organs. In some embodiments, organ pirfenidone levels may also mimic
that of plasma, such as for example, the lung, heart, kidney or nervous system. In some
embodiments, delivery of about or greater than 0.004 mcg to 0.7 mcg pirfenidone to one
30 gram tissue may provide a similar therapeutic benefit to other organs. In some embodiments,
providing additional pirfenidone or pyridone analog may provide additional efficacy. In

02 May 2016
2012212269

some embodiments, this may be accomplished by inhalation (i.e. oral inhalation or intranasal inhalation) delivery of aerosolized pirfenidone or pyridone analog to the lung. In some embodiments, pirfenidone or pyridone analog delivered to the lung may, in some embodiments, become readily available to the heart. In some embodiments, providing about 5 0.1 mcg/mL to about 5 mcg/mL ELF or 0.004 mcg/gram to about 0.7 mcg/gram lung tissue pirfenidone or pyridone analog pyridone analog to the ELF or 0.2 to 0.7 mcg/gram lung tissue pirfenidone or pyridine analog may result in a similar efficacious dose to the heart in the absence of elevated systemic adverse events or toxicities observed with oral dosing. In some embodiments, intranasal inhalation or oral inhalation delivery of aerosolized 10 pirfenidone or pyridone analog to the lung may result in efficacious delivery of pirfenidone or pyridone analog to the liver. In some embodiments, pirfenidone or pyridone analog delivered to the lung will become available to the liver. In some embodiments, providing about 0.1 mcg/mL to about 5 mcg/mL ELF or 0.004 mcg/gram to about 0.7 mcg/gram lung tissue pirfenidone or pyridone analog pyridone analog may result in a similar efficacious dose to the 15 liver in the absence of elevated systemic adverse events or toxicities observed with oral dosing. In some embodiments, intranasal or oral inhalation delivery of aerosolized pirfenidone or pyridone analog to the lung may result in efficacious delivery of pirfenidone or pyridone analog to the kidney. In some embodiments, pirfenidone or pyridone analog delivered to the lung will become available to the kidney. In some embodiments, providing 20 about 0.1 mcg/mL to about 5 mcg/mL ELF or 0.004 mcg/gram to about 0.7 mcg/gram lung tissue pirfenidone or pyridone analog pyridone analog may result in a similar efficacious dose to the kidney in the absence of elevated systemic adverse events or toxicities observed with oral dosing. In some embodiments, intranasal inhalation delivery of aerosolized pirfenidone or pyridone analog to the nasal cavity may result in efficacious delivery of pirfenidone or 25 pyridone analog to the central nervous system (CNS). In some embodiments, inhalation delivery of pirfenidone or pyridone analog to the nasal cavity will become readily available to the CNS. In some embodiments, providing a nasal cavity-delivered dose equivalent to about 0.1 mcg/mL to about 5 mcg/mL ELF or 0.004 mcg/gram to about 0.7 mcg/gram lung tissue pirfenidone or pyridone analog may result in similar efficacy in the CNS in the absence 30 elevated systemic adverse events or toxicities observed with oral dosing.

02 May 2016
2012212269

In some embodiments, topical delivery of aerosolized, liquid or cream pirfenidone or pyridone analog to a site of desired effect providing about 0.004 mcg/gram to about 0.7 mcg/gram tissue weight may result in a similar efficacious dose in the absence of systemic adverse events or toxicities. In some embodiments, topical delivery of aerosolized, liquid or cream pirfenidone or pyridone analog to damaged skin epithelium may prevent or reverse scarring, fibrosis and/or inflammation. This damage could be the result of infection, burn, surgery, acute or chronic injury (such as bed soars), or other event. In some embodiments, topical delivery of liquid or dry powder pirfenidone or pyridone analog to the bladder may prevent scarring, fibrosis and/or inflammation associated with bladder infection, bladder cancer, in-dwelling catheter or other event. In some embodiments, topical delivery of liquid pirfenidone or pyridone analog to the eye may prevent development of post-operative fibrosis in the conjunctiva and/or episclera following glaucoma surgery.

In some embodiments, injection delivery of liquid pirfenidone or pyridone analog to a site of desired effect providing about 0.004 mcg/gram to about 0.7 mcg/gram tissue weight pirfenidone or pyridone analog may result in a similar efficacious dose in the absence of systemic adverse events or toxicities. In some embodiments, injection delivery of liquid pirfenidone or pyridone analog to skeletal joints may prevent scarring, fibrosis and/or inflammation associated with autoimmune diseases, arthritis, rheumatoid arthritis, infection or other event.

In some embodiments, in addition to C_{max}, and in additional embodiments, pirfenidone exposure (AUC) to the disease site may also be critical for efficacy. In some embodiments, plasma AUC_{0-infinity} about or greater than 50 mg·hr/L is also associated with pulmonary efficacy. In some embodiments, partial or ready equilibrium of pirfenidone between the plasma and lung ELF and between the plasma and lung tissue, in some embodiments, may provide that AUC may also be mimicked in the lung. In other embodiments, lung ELF and tissue AUC may be less.

In some embodiments, individually or in combination C_{max}, AUC and/or half-life are required for efficacy, and thus in some embodiments are provided a conservative model with all three parameters (C_{max}, AUC and half-life) required for efficacy. In some embodiments, and by non-limiting example, direct inhalation delivery of about 0.1 mcg to about 5 mcg pirfenidone or pyridone analog to one mL lung ELF, providing an ELF AUC_{0-infinity} about 1.0

02 May 2016
2012212269

mg-hr/L or about 50 mg-hr/L, and maintaining these levels for the same period of time as that delivered via the oral route are equivalently efficacious. Similarly, in other embodiments, direct inhalation delivery of about or greater than 0.2004 to 0.7 mcg pirfenidone or pyridone analog to one gram lung tissue, provides a tissue $AUC_{0-\infty}$ less than to equivalent or substantially equivalent to that of the plasma following oral delivery, and in further embodiments, maintaining these levels for the same period of time as that delivered via the oral route is equivalently efficacious. In some embodiments, the following assumptions and theoretical calculations are described for inhalation therapy:

ELF Delivery Assumptions:

1. The total volume of human ELF is 25 mL;
2. The inhaled route of administration is dependent upon a respirable delivered dose (RDD); RDD is the fraction of drug inhaled in aerosol particles less than 5 microns in diameter;

3. RDD of typical dry powder, liquid nebulization or meter-dose inhalation devices ranges from 10% to 70%. In some embodiments, higher and lower efficiency devices with RDDs greater than 70% and less than 10% are contemplated.

4. Plasma pirfenidone or pyridone analog half-life following oral administration is around 2.5 hours. In some embodiments, intestinal absorption affects this value but for exemplary purposes of this model the lung ELF pirfenidone half-life following inhalation delivery is assumed to be one-half that following oral administration (e.g. $2.5 \text{ hours}/2 = 1.25 \text{ hours}$). Half-life values may be supported by measurements indicating intravenous administration of pirfenidone results in a lung ELF half-life of around one-half that following oral administration;

5. In some embodiments, a lung ELF level of 5 mcg/mL may be the lower limit of efficacy; and

6. 801 mg oral pirfenidone results in a plasma level at or greater than 5 mcg/mL for 4 hours (human-measured value). For purposes of comparing routes, this model will assume lung ELF pirfenidone levels following oral administration remain at or above 5 mcg/mL lung ELF for the same duration as plasma.

Exemplary ELF Calculations:

02 May 2016
2012212269

1. Mcg pirfenidone delivered to 25 mL ELF to make 5 mcg/mL = 125 mcg;
2. Based upon an RDD efficiency of 30%, the unit dose required is 416 mcg ($125 \text{ mcg} / 0.3 = 416 \text{ mcg}$);
3. Based upon an RDD efficiency of 50%, the unit dose required is 250 mcg ($125 \text{ mcg} / 0.5 = 250 \text{ mcg}$);
4. Based upon an RDD efficiency of 70%, the unit dose required is 179 mcg ($125 \text{ mcg} / 0.7 = 179 \text{ mcg}$); and

Compensating to maintain at or above these levels for 3.2 half lives of 1.25

hours each (4 hours at or above 5 mcg/mL with a lung half-life of 1.25 hours = 3.2 half lives):

5. For an RDD efficiency of 30%, the unit dose required to maintain the lower limit of clinically-observed efficacy (in this case 416 mcg) for 3.2 half lives is 3994 mcg;
6. For an RDD efficiency of 50%, the unit dose required to maintain the lower limit of clinically-observed efficacy (in this case 250 mcg) for 3.2 half lives 2400 mcg; and
7. For an RDD efficiency of 70%, the unit dose required to maintain the lower limit of clinically-observed efficacy (in this case 179 mcg) for 3.2 half lives 1718 mcg.

By non-limiting example, based upon the above assumptions and in certain embodiments, a dose of approximately 4 mg in a device delivering pirfenidone or pyridone analog with 30% efficiency may result in lung ELF levels at or above 5 mcg/mL for the same duration as that obtained following 801 mg administered orally. Moreover, while the minimally efficacious pirfenidone dose may be maintained for this duration, local pirfenidone levels may also exhibit significantly higher ELF Cmax levels providing improved efficacy. In some embodiments, delivery of 4 mg pirfenidone or pyridone analog with a 30% efficiency device may result in a lung ELF Cmax up to about 48 mcg/mL ($4 \text{ mg} \times 30\% = 1.2 \text{ mg}$. $1.2 \text{ mg} / 25 \text{ mL ELF} = 48 \text{ mcg/mL}$). In some embodiments, based upon the above assumptions a dose of approximately 66 mg in a device delivering pirfenidone or pyridone analog with 70% efficiency may result in a lung ELF Cmax up to 1.85 mg/mL ($66 \text{ mg} \times 70\% = 46.2 \text{ mg}$. $46.2 \text{ mg} / 25 \text{ mL ELF} = 1.85 \text{ mg/mL}$). In some embodiments, based upon the

02 May 2016
2012212269

above assumptions a dose of approximately 154 mg in a device delivering pirfenidone or pyridone analog with 30% efficiency may also result in a lung ELF Cmax up to 1.85 mg/mL ($154 \text{ mg} \times 30\% = 46.2 \text{ mg}$. $46.2 \text{ mg}/25 \text{ mL ELF} = 1.85 \text{ mg/mL}$). In some embodiments, based upon the above assumptions a dose of approximately 12 mg in a device delivering pirfenidone or pyridone analog with 70% efficiency may result in a lung ELF Cmax up to 336 mcg/mL ($12 \text{ mg} \times 70\% = 8.4 \text{ mg}$. $8.4 \text{ mg}/25 \text{ mL ELF} = 336 \text{ mcg/mL}$). In some embodiments, based upon the above assumptions a dose of approximately 28 mg in a device delivering pirfenidone or pyridone analog with 30% efficiency may also result in a lung ELF Cmax up to 336 mcg/mL ($28 \text{ mg} \times 30\% = 8.4 \text{ mg}$. $8.4 \text{ mg}/25 \text{ mL ELF} = 336 \text{ mcg/mL}$). In some embodiments, this dose may result in maintaining at or above the 5 mcg/mL minimally efficacious dose for about 6 half-lives, or about 15 hours. In some embodiments, the embodiments described for inhalation therapy provide beneficial efficacy through an increased Cmax and maintaining drug exposure at or above the 5 mcg/mL minimal efficacy range for a longer duration than that currently limited by oral dosing. In some embodiments, prolonged exposure may enable a reduced dosing interval (by example once-a-day or twice-a-day versus the current three times a day oral dosing regimen). In some embodiments, while delivery is directly to the lung, these doses may result in very low systemic plasma levels (e.g. around 2 mcg/mL pirfenidone). In some embodiments, although about 28 mg pirfenidone or pyridone analog delivered with a 30% efficiency aerosol device may initially result in elevated levels in vasculature and tissues immediately downstream of the lung (or nasal cavity), the dilute systemic plasma concentration may be around 1.7 mcg/mL ($28 \text{ mg} \times 30\% = 8.4 \text{ mg}$. $8.4 \text{ mg} / 5 \text{ L total body blood} = 1.7 \text{ mcg/mL}$). In some embodiments, delivery of about 46 mg pirfenidone or pyridone analog may result in a dilute systemic plasma concentration of about 9.3 mcg/mL.

One of skill in the art will recognize from the discussions herein that doses calculated in the above model will change if the actual measured lung ELF half-life of pirfenidone or pyridone analog elimination changes. If the half-life is shorter, more administered pirfenidone or pyridone analog will be required to maintain the lung ELF concentration above that considered the minimal efficacious level. Additional increases in administered pirfenidone or pyridone analog may be desired to further improve efficacy. Further, in addition to delivering desired lung tissue Cmax and AUC, oral inhaled or

02 May 2016
2012212269

intranasal inhaled delivery of aerosol pirfenidone or pyridone analog may also serve an efficient route for systemic delivery. In some embodiments, dosing schemes are contemplated that enable inhaled delivery of pirfenidone or pyridone analog to initially achieve desired lung tissue C_{max} and AUC, with plasma half-life slower than that of the lung ELF, and targeting the delivery of specific plasma concentrations may in turn prolong lung ELF-pirfenidone or pyridone analog exposure.

Exemplary Lung Tissue Delivery Assumptions:

1. The total wet weight of the adult human lung is about 685 to 1,050 grams (for calculations, conservatively about 1,000 grams);

2. The adult human lung blood volume is about 450 mL;

3. The tissue weight of the adult human lung is conservatively 1,050 grams wet weight minus 450 mL blood weight (assuming density of 1.0), equals 600 grams;

4. In some embodiments, following intravenous push of pirfenidone to a mouse:

- plasma pirfenidone T_{max} is equivalent to lung T_{max}

- 40 mg/kg intravenous dose results in plasma C_{max} of about 55 mcg/mL and a lung C_{max} of 30 mcg/gram wet tissue

- Conservatively, blood makes up about 40% of the wet lung weight.

Given that the plasma and lung T_{max} are, in some embodiments, equivalent, it follows that much of the 30 mcg/g pirfenidone measured in the wet lung is due to the presence of blood.

Conservatively, if blood makes up about 40% of the wet lung weight, then 40% of the plasma C_{max} (or 55 mcg/mL X 40%) is about 22 mcg/gram pirfenidone in the measured lung weight is due to blood. Taking the difference between the wet lung C_{max} and this number (or 30 mcg/g minus 22 mcg/g), about 8 mcg/g is in the lung tissue.

- a measured wet lung half-life that is about 45% longer than the plasma half-life may be considered. Taking the argument above that about 40% of the wet lung pirfenidone is in the blood, the actual lung tissue half-life is much greater than 45% longer than plasma;

5. From the above observations and calculations that 55 mcg/mL plasma C_{max} results in a lung tissue C_{max} of about 8 mcg/gram, the following comparison to humans can be made:

02 May 2016
2012212269

- Taking an early assumption, the lower end of human efficacy is 5 mcg/mL plasma pirfenidone.

- Assuming the above ratio (55 mcg/mL plasma results in 8 mcg/gram lung tissue) is true for humans, 5 mcg/mL divided by 55 mcg/mL is about 9.1%. 9.1% of 8 mcg/gram is about 0.7 mcg/gram.

- Taken together, 5 mcg/mL plasma pirfenidone may result in 0.7 mcg/gram lung tissue pirfenidone. Thus, about 0.7 mcg/gram lung tissue pirfenidone is the lower end of efficacy.

6. The inhaled route of administration is dependent upon a respirable delivered dose (RDD). The RDD is the fraction of drug inhaled in aerosol particles less than 5 microns in diameter;

7. RDD of typical dry powder, liquid nebulization or meter-dose inhalation devices ranges from 10% to 70%. Higher and lower efficiency devices with RDDs greater than 70% and less than 10% also exist;

8. As discussed above, lung tissue pirfenidone half-life is much longer than the intravenously delivered plasma pirfenidone half-life (by as much or greater than 2-4X). Plasma pirfenidone half-life following oral administration is around 2.5 hours. However, continued intestinal absorption affects this number and hence is much longer than that following intravenous delivery. Therefore, for purposes of this model the lung tissue pirfenidone half-life following inhalation delivery will be considered equivalent to that following oral administration (e.g. 2.5 hours);

9. From the above observations and calculations, the lower limit of efficacy in lung tissue is 8 mcg/gram; and

10. Incorporating that 801 mg oral pirfenidone results in a human plasma level at or greater than 5 mcg/mL for 4 hours and that 5 mcg/mL plasma results in 0.7 mcg/gram lung tissue pirfenidone, what is delivered by oral or intranasal inhalation must be at or above 0.7 mcg/gram lung tissue pirfenidone for at least 4 hours for equivalent lung fibrosis efficacy to the oral dose.

Exemplary Lung Tissue Calculations:

1. Mcg pirfenidone delivered to 1000 grams wet lung tissue (blood plus lung tissue) to make 0.7 mcg/gram = 700 mcg;

02 May 2016
2012212269

2. Based upon an RDD efficiency of 30%, the unit dose required is 2,333 mcg ($700 \text{ mcg} / 0.3 = 2,333 \text{ mcg}$);
3. Based upon an RDD efficiency of 50%, the unit dose required is 1,400 mcg ($700 \text{ mcg} / 0.5 = 1,400 \text{ mcg}$);
4. Based upon an RDD efficiency of 70%, the unit dose required is 1,000 mcg ($700 \text{ mcg} / 0.7 = 1,000 \text{ mcg}$); and

Compensating to maintain at or above these levels for 2 half lives of 2.5 hours each (4 hours at or above 0.7 mcg/gram wet lung tissue with a lung half-life of 2.5 hours = 1.6 half lives):

5. For an RDD efficiency of 30%, the unit dose required to match the lower limit of clinically-observed oral route efficacy (in this case 2,333 mcg) for 1.6 half lives is 3,733 mcg;
6. For an RDD efficiency of 50%, the unit dose required to match the lower limit of clinically-observed oral route efficacy (in this case 1,400 mcg) for 1.6 half lives 2,240 mcg; and
7. For an RDD efficiency of 70%, the unit dose required to match the lower limit of clinically-observed oral route efficacy (in this case 1,000 mcg) for 1.6 half lives 1,600 mcg.

By non-limiting example, based upon the above assumptions a dose of approximately 3.7 mg in a device delivering pirfenidone or pyridone analog with 30% efficiency may result in wet lung tissue levels at or above 0.7 mcg/gram for the same duration as that obtained following 801 mg administered orally. Moreover, while the minimally efficacious pirfenidone dose is maintained for this duration, local pirfenidone levels may exhibit significantly higher wet lung tissue Cmax levels providing improved efficacy. By non-limiting example, delivery of 3.7 mg pirfenidone or pyridone analog with a 30% efficiency device may result in a wet lung tissue Cmax up to about 1.1 mcg/gram ($3.7 \text{ mg} \times 30\% = 1.1 \text{ mg}$. $1.1 \text{ mg} / 1,050 \text{ grams wet lung weight} = 1.1 \text{ mcg/gram}$). This number is near about 1.5-fold higher than that delivered following oral delivery. By another non-limiting example, based upon the above assumptions a dose of approximately 50 mg in a device delivering pirfenidone or pyridone analog with 30% efficiency may result in a wet lung tissue Cmax up to 14.3 mcg/mL ($50 \text{ mg} \times 30\% = 15 \text{ mg}$. $15 \text{ mg} / 1,050 \text{ grams wet lung weight} = 14.3$

02 May 2016
2012212269

mcg/gram), or about 20-fold higher than that delivered following oral delivery. Under this scenario, this dose may result in maintaining at or above the 0.7 mcg/gram wet lung tissue minimally efficacious dose for at least about 5 half-lives, or about 12.5 hours; compared to 4 hours following 801 mg oral dose administration. Similarly, by another non-limiting

5 example, based upon the above assumptions a dose of approximately 15 mg in a device delivering pirfenidone or pyridone analog with 70% efficiency may result in a wet lung tissue Cmax up to 10 mcg/mL ($15 \text{ mg} \times 70\% = 10.5 \text{ mg}$. $10.5 \text{ mg}/1,050 \text{ grams wet lung weight} = 10 \text{ mcg/gram}$), or about 14-fold higher than that delivered following oral delivery. Under this scenario, this dose may result in maintaining at or above the 0.7 mcg/gram wet lung tissue

10 minimally efficacious dose for about 4.5 half-lives, or at least about 11 hours; compared to 4 hours following 801 mg oral dose administration. Such duration over 0.7 mcg/gram lung tissue may permit twice a day dosing (BID). Similarly, by another non-limiting example, based upon the above assumptions a dose of approximately 75 mg in a device delivering pirfenidone or pyridone analog with 70% efficiency may result in a wet lung tissue Cmax up

15 to 50 mcg/mL ($75 \text{ mg} \times 70\% = 52.5 \text{ mg}$. $52.5 \text{ mg}/1,050 \text{ grams wet lung weight} = 50 \text{ mcg/gram}$), or about 71-fold higher than that delivered following oral delivery. Under this scenario, this dose may result in maintaining at or above the 0.7 mcg/gram wet lung tissue minimally efficacious dose for at least about 6 half-lives, or about 15 hours; compared to 4 hours following 801 mg oral dose administration. Such duration over 0.7 mcg/gram lung

20 tissue may permit BID dosing. Similarly, by another non-limiting example, based upon the above assumptions a dose of approximately 15 mg in a device delivering pirfenidone or pyridone analog with 30% efficiency may result in a wet lung tissue Cmax up to 4.3 mcg/mL ($15 \text{ mg} \times 30\% = 4.5 \text{ mg}$. $4.5 \text{ mg}/1,050 \text{ grams wet lung weight} = 4.3 \text{ mcg/gram}$), or about 6-fold higher than that delivered following oral delivery. Under this scenario, this dose may

25 result in maintaining at or above the 0.7 mcg/gram wet lung tissue minimally efficacious dose for at least about 3 half-lives, or about 7.5 hours; compared to 4 hours following 801 mg oral dose administration. Similarly, by another non-limiting example, based upon the above assumptions a dose of approximately 75 mg in a device delivering pirfenidone or pyridone analog with 30% efficiency may result in a wet lung tissue Cmax up to 21 mcg/mL ($75 \text{ mg} \times$

30 $30\% = 22.5 \text{ mg}$. $52.5 \text{ mg}/1,050 \text{ grams wet lung weight} = 21 \text{ mcg/gram}$), or about 31-fold higher than that delivered following oral delivery. Under this scenario, this dose may result

02 May 2016
2012212269

in maintaining at or above the 0.7 mcg/gram wet lung tissue minimally efficacious dose for at least about 5 half-lives, or about 12.5 hours; compared to 4 hours following 801 mg oral dose administration. Such duration over 0.7 mcg/gram lung tissue may permit BID dosing.

Similarly, by another non-limiting example, based upon the above assumptions a dose of

approximately 15 mg in a device delivering pirfenidone or pyridone analog with 10% efficiency may result in a wet lung tissue Cmax up to 1.4 mcg/mL ($15 \text{ mg} \times 10\% = 1.5 \text{ mg}$. $1.5 \text{ mg} / 1,050 \text{ grams wet lung weight} = 1.4 \text{ mcg/gram}$), or about 2-fold higher than that delivered following oral delivery. Under this scenario, this dose may result in maintaining at or above the 0.7 mcg/gram wet lung tissue minimally efficacious dose for about 1 half-lives, or at least about 2.5 hours; compared to 4 hours following 801 mg oral dose administration.

Similarly, by another non-limiting example, based upon the above assumptions a dose of approximately 75 mg in a device delivering pirfenidone or pyridone analog with 10% efficiency may result in a wet lung tissue Cmax up to 21 mcg/mL ($75 \text{ mg} \times 10\% = 7.5 \text{ mg}$. $7.5 \text{ mg} / 1,050 \text{ grams wet lung weight} = 7.1 \text{ mcg/gram}$), or about 10-fold higher than that

delivered following oral delivery. Under this scenario, this dose may result in maintaining at or above the 0.7 mcg/gram wet lung tissue minimally efficacious dose for about 3.5 half-lives, or at least about 8.8 hours; compared to 4 hours following 801 mg oral dose administration.

Such duration over 0.7 mcg/gram lung tissue may permit TID dosing. Such an approach could benefit efficacy through an increased Cmax and maintaining drug exposure at or above the 0.7 mcg/gram wet lung tissue minimal efficacy range for a longer duration than that currently limited by oral dosing. Such prolonged exposure may enable a reduced dosing

interval (by example once-a-day or twice-a-day versus the current three times a day oral dosing regimen). Moreover, while this approach delivers directly to the lung, using the above non-limiting examples these doses may result in reduced systemic plasma levels (e.g. Cmax from less than 0.6 mcg/mL pirfenidone from a 4.5 mg delivered dose to 5,000 mL blood to less than 2 mcg/mL pirfenidone from a 15 mg delivered dose to less than 10 mcg/mL from a 75 mg dose).

Doses calculated in the above model will change considerably if the actual measured lung tissue half-life of pirfenidone or pyridone analog elimination changes. If the half-life is faster, more inhaled pirfenidone or pyridone analog will be required to maintain the lung tissue concentration above that considered the minimal efficacious level. Additional

02 May 2016
2012212269

increases in inhaled pirfenidone or pyridone analog may be desired to further improve efficacy. Further, in addition to delivering desired lung tissue Cmax and AUC, inhaled delivery of aerosol pirfenidone or pyridone analog may also serve an efficient route for systemic delivery. In some embodiments, dosing schemes are contemplated that enable

5 inhaled delivery of pirfenidone or pyridone analog to initially achieve desired lung tissue Cmax and AUC, and as plasma half-life is predicted to be slower than that of the lung tissue, targeting the delivery of specific plasma concentrations may in turn prolong lung tissue-pirfenidone or pyridone analog exposure.

As scarring is irreversible, IPF efficacy is the act of protecting native lung tissue

10 against invading fibrosis. Therefore, maintaining regular efficacious drug levels in unaffected tissue is critical for improved patient survival. Clinical and nonclinical studies have suggested pirfenidone efficacy is dose-responsive ranging from slowed-disease progression to improvement. Unfortunately, substantial gastrointestinal (GI) side effects and systemic toxicity have forced an approved oral dose that is limited to the lower end of this range.

15 Complicating matters, recommendations for dose-absorbing food and frequent triggering of dose-reduction/discontinuation protocols addressing these issues further reduce lung dose and interrupt required maintenance therapy of this otherwise promising drug. Inhalation delivery of aerosol pirfenidone or pyridone analog directly to the lung will reduce or eliminate these safety or tolerability limitations associated with the oral route of delivery.

20 Oral pirfenidone efficacy has been moderately demonstrated in human clinical studies and the data suggests that this effect increases with higher doses. Unfortunately, significant side effects and toxicity have limited the oral dose to the lower end of this efficacy range (Esbriet approved up to 2403 mg/d). Jeopardizing this already low efficacy dose, the Esbriet prescription requires an initial dose-escalation scheme and recommended administration with

25 food to acquire minimal GI tolerance and an acceptable side-effect/toxicity profile (range up to three 267 mg capsules, or 801 mg three times a day (TID)). Unfortunately, not all patients reach this recommended dose and food further reduces bioavailability (food reduces Cmax and AUC ~50% and ~20%, respectively). Further, elevated liver enzyme levels and skin photoreactivity initiate a physician-guided dose-reduction and stoppage protocol that in Phase

30 3 studies permitted up to a 50% dose reduction before discontinuation (in these studies between 48% and 67% of patient doses were reduced). As chronic lung tissue dosing of

02 May 2016
2012212269

effective drug levels is critical for maintenance protection against invading fibrosis, it is likely that oral pirfenidone prescription and practice result in sub-efficacious dosing of this otherwise promising drug; a hypothesis that may in part explain the moderate efficacy observed in Phase 3 studies.

5 For oral administration in the context of treatment of pulmonary fibrosis high oral doses are required to achieve plasma levels required for efficacious lung tissue exposure. However, gastrointestinal side-effects and systemic toxicities have limited the approved oral dose to a level restricted to the low end of the efficacy and dose-response curve. In one embodiment, inhaled pirfenidone or pyridone analog improves pirfenidone treatment
10 effectiveness through increased lung dose and improved compliance. In one embodiment, inhalation of pirfenidone or pyridone analog (e.g. with a nebulizer) delivers pirfenidone or pyridone analog directly to the lung and whole-body dilution of the delivered dose is minimized. In some embodiments, inhalation of pirfenidone reduces or eliminates GI
15 exposure and/or systemic toxicities that are common with oral administration of pirfenidone or pyridone analog. In some embodiments, inhalation delivery of pirfenidone or pyridone analog provided herein provides higher lung tissue levels of pirfenidone than is possible through oral administration. In some embodiments, inhalation delivery of pirfenidone or
20 pyridone analog serves as an efficient means of delivering pirfenidone or pyridone analog to the systemic compartment. In some embodiments, inhalation delivery of pirfenidone or pyridone analog provides Cmax and AUC benefits over the oral route. In some
embodiments, inhalation delivery of pirfenidone or pyridone analog provides Cmax and AUC benefits over the oral route, wherein plasma re-circulated, aerosol-delivered pirfenidone or
25 pyridone analog maintains these beneficial properties. In some embodiments, the methods described herein may be used to treat patients diagnosed with mild-to-moderate IPF. In some
embodiments, the methods described herein may be used to treat patients diagnosed with
mild-to-severe IPF. In some embodiments, the methods described herein may be used to treat
patients diagnosed with mild-to-moderate IPF without the need to initially dose-escalate the
patient. In some embodiments, the methods described herein may be used to treat patients
30 diagnosed with mild-to-severe IPF without the need to initially dose-escalate the patient. In
some embodiments, the methods described herein may be used to treat patients diagnosed
with mild-to-moderate IPF without the need to monitor and dose-reduce or stop therapy due

02 May 2016
2012212269

to gastrointestinal, phototoxic or liver enzyme-associated adverse events. In some
embodiments, the methods described herein may be used to treat patients diagnosed with
mild-to-severe IPF without the need to monitor and dose-reduce or stop therapy due to
gastrointestinal, phototoxic or liver enzyme-associated adverse events. In some
5 embodiments, the methods described herein may be used to provide a prophylactic therapy to
patients diagnosed with mild-to-moderate IPF. In some embodiments, the methods described
herein may be used to provide a prophylactic therapy to patients diagnosed with mild-to-
severe IPF. In some embodiments, the methods described herein may be used to provide a
prophylactic therapy to patients with mild-to-moderate IPF without the need to initially dose-
10 escalate the patient. In some embodiments, the methods described herein may be used
provide a prophylactic therapy to patients diagnosed with mild-to-severe IPF without the
need to initially dose-escalate the patient. In some embodiments, the methods described
herein may be used to provide a prophylactic therapy to patients diagnosed with mild-to-
moderate IPF without the need to monitor and dose-reduce or stop therapy due to
15 gastrointestinal, phototoxic or liver enzyme-associated adverse events. In some
embodiments, the methods described herein may be used to provide a prophylactic therapy to
patients diagnosed with mild-to-severe IPF without the need to monitor and dose-reduce or
stop therapy due to gastrointestinal, phototoxic or liver enzyme-associated adverse events. In
some embodiments, the methods described herein may be used to slow disease progression of
20 patients diagnosed with mild-to-moderate IPF without the need to initially dose-escalate the
patient. In some embodiments, the methods described herein may be used to slow disease
progression of patients diagnosed with mild-to-severe IPF without the need to initially dose-
escalate the patient. In some embodiments, the methods described herein may be used to
slow disease progression of patients diagnosed with mild-to-moderate IPF without the need to
25 monitor and dose-reduce or stop therapy due to gastrointestinal, phototoxic or liver enzyme-
associated adverse events. In some embodiments, the methods described herein may be used
to slow disease progression of patients diagnosed with mild-to-severe IPF without the need to
monitor and dose-reduce or stop therapy due to gastrointestinal, phototoxic or liver enzyme-
associated adverse events. By non-limiting example, clinical end points of IPF efficacy
30 include reduced decline in forced vital capacity (FVC), reduced decline in distance walked
over a six-minute interval (six-minute walk test; 6MWT), slowed decline in carbon monoxide

diffusion capacity (DL_{CO}), improved progression-free survival (PFS), reduced mortality and monitoring changes in biomarkers such as MMP7, and CCL18. In some embodiments, a comparison of oral and inhaled aerosol properties that may be observed is shown in Table A.

Table A. Advantages of inhaling pirfenidone

Oral Pirfenidone	Inhaled Pirfenidone
High oral dose = minimally-effective lung levels	Lower inhaled dose = superior lung levels
Oral route = significant GI side effects	Inhaled route = no/reduced GI side effects
High dose = toxicity	Lower dose = reduced toxicity
<u>Low efficacy:</u> <ol style="list-style-type: none"> 1. Pirfenidone is a low potency drug. The oral route requires a very high dose to deliver sufficient lung levels. Significant GI side effects and to a lesser extent systemic toxicities limit the oral dose to the lower end of the efficacy and dose-response curve. 2. Initial dose escalation required to obtain maximum-tolerated maintenance dose. Due to poor tolerability, this maintenance dose is often <u>set below</u> the approved dose level 3. <u>Continued intolerability and safety concerns reduce adherence to maintenance therapy</u> <ul style="list-style-type: none"> • Dose reduced and interrupted <ul style="list-style-type: none"> - Recommended food absorbs drug - Side effects and toxicity trigger dose reduction/stoppage protocols 	<u>High efficacy:</u> <ol style="list-style-type: none"> 1. Inhaled route permits use of smaller pirfenidone doses to deliver superior initial pirfenidone lung tissue C_{max} and AUC in the absence of GI side-effects. In some embodiments, inhaled administration also serves as non-oral route for systemic delivery; enabling sufficient circulating plasma pirfenidone levels to extend the duration of superior efficacy. 2. Good tolerability permits establishing the maintenance dose at the approved level 3. <u>Strong adherence</u> to maintenance therapy <ul style="list-style-type: none"> • Dose and chronic therapy maintained <ul style="list-style-type: none"> - Inhaled drug unaffected by food - Safe & well-tolerated; no need for special protocols

In some embodiments the methods described herein provide for delivery of high concentration, readily bioavailable pirfenidone or pyridone analog compound which in turn provides improved efficacy over pirfenidone or pyridone analog compound administered by the oral route or by inhalation of a slow-dissolving or otherwise slowly bioavailable compound formulation. In some embodiments, such slow-dissolving or otherwise slowly bioavailable compound formulations for inhalation include, but are not limited to a dry powder formulation, a liposomal formulation, a nano-suspension formulation, or a micro-

02 May 2016
2012212269

suspension formulation. In some embodiments, the aqueous solutions of pirfenidone or pyridone analog described and contemplated herein for administration by inhalation are completely homogeneous and soluble.

In some embodiments, an obstacle to patient compliance with oral pirfenidone therapy is GI intolerability. Pirfenidone blood levels may also be important as they have been implicated in other observed toxicities. Thus, factors contributing to increased blood levels must be considered. For the oral route of administration, toxicity and GI intolerability have limited the dose to 801 mg three times a day. While elevated liver enzymes, photosensitivity reaction and phototoxicity occur at this dose, they occur with higher frequency and greater severity with higher doses. Secondly, pirfenidone is primarily metabolised by CYP1A2. *In vitro* metabolism studies with hepatic microsomes indicate that approximately 48% of pirfenidone is metabolised via CYP1A2 with other CYP isoenzymes including CYP2C9, 2C19, 2D6, and 2E1 each contributing less than 13%. Thus, inhibiting these enzyme systems results in elevated pirfenidone blood levels, resulting in increased incidence and severity of toxicity. To this end, items such as grapefruit juice, fluvoxamine and other inhibitors of CYP1A2 should be avoided during oral treatment with pirfenidone.

Oral administration of pirfenidone is contraindicated in patients with concomitant use of fluvoxamine. Fluvoxamine should be discontinued prior to the initiation of Esbriet therapy and avoided during Esbriet therapy due to the reduced clearance of pirfenidone. Other therapies that are inhibitors of both CYP1A2 and one or more other CYP isoenzymes involved in the metabolism of pirfenidone (e.g. CYP2C9, 2C19, and 2D6) should also be avoided during pirfenidone treatment.

Also for the oral administration, special care should also be exercised if CYP1A2 inhibitors are being used concomitantly with potent inhibitors of one or more other CYP isoenzymes involved in the metabolism of pirfenidone such as CYP2C9 (e.g. amiodarone, fluconazole), 2C19 (e.g. chloramphenicol) and 2D6 (e.g. fluoxetine, paroxetine).

The oral product should be used with caution in patients treated with other moderate or strong inhibitors of CYP1A2 (e.g. ciprofloxacin, amiodarone, propafenone).

As many products affecting CYP enzymes are useful to fibrosis patients, permitting their use would be beneficial. While the oral route is already at the maximum permissible dose (which provides only moderate efficacy), any inhibition of the enzymes described above

02 May 2016
2012212269

elevates pirfenidone blood levels and increases the rate and severity of the toxic events described herein. In some embodiments oral inhalation and intranasal inhalation delivery of pirfenidone or pyridone analogs can achieve effective tissue levels with much less drug than that required by the oral product, and in some embodiments result in blood levels are significantly lower and consequences associated with CYP enzyme inhibitory properties described herein are removed. In some embodiments, use of these CYP inhibitory enzyme products currently contraindicated with the oral medicine may be administered with pirfenidone or pyridone analog.

The primary metabolite of pirfenidone is 5-carboxy-pirfenidone. Following oral or intravenous administration, this metabolite appears quickly at high concentrations in blood. 5-carboxy-pirfenidone does not appear to have anti-fibrotic or anti-inflammatory activity, its high blood levels occur at the loss of pirfenidone blood concentrations. Thus, while the oral product is dosed at the highest possible level, once pirfenidone enters the blood it is rapidly metabolized to a non-active species further reducing the drugs potential to achieve sufficient lung levels required for substantial efficacy. In some embodiments, because oral inhalation and intranasal inhalation delivery of pirfenidone or pyridone analogs can achieve effective lung tissue levels directly, extra-lung metabolism is minimized.

In some embodiments, administration of pirfenidone or pyridone analog compound by inhalation has reduced gastrointestinal side-effects when compared to oral administration. In some embodiments, the reduced gastrointestinal side-effects with administration by inhalation avoids the need for initial dose-escalation. In some embodiments, administration of pirfenidone or pyridone analog by inhalation avoids or substantially avoids the gastrointestinal tract and therefore effects observed with oral administration of pirfenidone or pyridone analog compound will be minimized or not present. In some embodiments, the lack of food effects with administration by inhalation will allow for full dose delivery.

In some embodiments, pharmaceutical compositions described herein are used in the treatment of lung disease in mammal. In some embodiments, the pharmaceutical compositions described herein are administered to a mammal by oral inhalation or intranasal inhalation methods for the purpose of treating lung disease in the mammal. In some embodiments, lung disease includes, but is not limited to, asthma, chronic obstructive pulmonary disease (COPD), pulmonary fibrosis, idiopathic pulmonary fibrosis, radiation

2012212269 02 May 2016

induced fibrosis, silicosis, asbestos induced pulmonary or pleural fibrosis, acute lung injury, acute respiratory distress syndrome (ARDS), sarcoidosis, usual interstitial pneumonia (UIP), cystic fibrosis, Chronic lymphocytic leukemia (CLL)-associated fibrosis, Hamman-Rich syndrome, Caplan syndrome, coal worker's pneumoconiosis, cryptogenic fibrosing alveolitis, 5 obliterative bronchiolitis, chronic bronchitis, emphysema, pneumonitis, Wegner's granulomatosis, lung scleroderma, silicosis, interstitial lung disease, asbestos induced pulmonary and/or pleural fibrosis. In some embodiments, lung disease is lung fibrosis (i.e. pulmonary fibrosis). In some embodiments, lung disease is idiopathic pulmonary fibrosis.

Pulmonary Fibrosis

10 In some embodiments, the compositions and methods described herein can treat or slow down the progression of or prevent pulmonary fibrosis. In some embodiments, pulmonary fibrosis includes interstitial pulmonary fibrosis. This group of disorders is characterized by scarring of deep lung tissue, leading to shortness of breath and loss of functional alveoli, thus limiting oxygen exchange. Etiologies include inhalation of inorganic 15 and organic dusts, gases, fumes and vapors, use of medications, exposure to radiation, and development of disorders such as hypersensitivity pneumonitis, coal worker's pneumoconiosis, radiation, chemotherapy, transplant rejection, silicosis, byssinosis and genetic factors

20 IPF as described herein refers to "idiopathic pulmonary fibrosis" and is in some embodiments a chronic disease that manifests over several years and is characterized by scar tissue within the lungs, in the absence of known provocation. Exercise-induced breathlessness and chronic dry cough may be the prominent symptoms. IPF belongs to a family of lung disorders known as the interstitial lung diseases (ILD) or, more accurately, the diffuse parenchymal lung diseases. Within this broad category of diffuse lung diseases, IPF 25 belongs to the subgroup known as idiopathic interstitial pneumonia (IIP). There are seven distinct IIPs, differentiated by specific clinical features and pathological patterns. IPF is the most common form of IIP. It is associated with the pathologic pattern known as usual interstitial pneumonia (UIP); for that reason, IPF is often referred to as IPF/UIP. IPF is usually fatal, with an average survival of approximately three years from the time of 30 diagnosis. There is no single test for diagnosing pulmonary fibrosis; several different tests

02 May 2016
2012212269

including chest x-ray, pulmonary function test, exercise testing, bronchoscopy and lung biopsy are used in conjunction with the methods described herein.

Idiopathic pulmonary fibrosis (also known as cryptogenic fibrosing alveolitis) is the most common form of interstitial lung disease, and may be characterized by chronic progressive pulmonary parenchymal fibrosis. It is a progressive clinical syndrome with unknown etiology; the outcome is frequently fatal as no effective therapy exists. In some embodiments, pirfenidone inhibits fibroblast proliferation and differentiation related to collagen synthesis, inhibits the production and activity of TGF-beta, reduces production of fibronectin and connective tissue growth factor, inhibits TNF-alpha and I-CAM, increase production of IL-10, and/or reduces levels of platelet-derived growth factor (PDGF) A and B in belomycin-induced lung fibrosis. The pirfenidone methods and compositions described herein may provide tolerability and usefulness in patients with advanced idiopathic pulmonary fibrosis and other lung diseases. In some embodiments, pirfenidone methods and compositions described herein may provide tolerability and usefulness in patients with mild to moderate idiopathic pulmonary fibrosis. In some embodiments, increased patient survival, enhanced vital capacity, reduced episodes of acute exacerbation (compared to placebo), and/or slowed disease progression are observed following pirfenidone treatment. In some embodiments inhaled delivery of pirfenidone or pyridone analog may be an effective means to prevent, manage or treat idiopathic pulmonary fibrosis or other pulmonary fibrotic diseases.

The term "pulmonary fibrosis", includes all interstitial lung disease associated with fibrosis. In some embodiments, pulmonary fibrosis includes the term "idiopathic pulmonary fibrosis" or "IPF". In some embodiments, pulmonary fibrosis, by non-limiting example, may result from inhalation of inorganic and organic dusts, gases, fumes and vapors, use of medications, exposure to radiation or radiation therapy, and development of disorders such as hypersensitivity pneumonitis, coal worker's pneumoconiosis, chemotherapy, transplant rejection, silicosis, byssinosis and genetic factors.

Exemplary lung diseases for the treatment or prevention using the methods described herein include, but are not limited, idiopathic pulmonary fibrosis, pulmonary fibrosis secondary to systemic inflammatory disease such as rheumatoid arthritis, scleroderma, lupus, cryptogenic fibrosing alveolitis, radiation induced fibrosis, chronic obstructive pulmonary

02 May 2016

2012212269

disease (COPD), sarcoidosis, scleroderma, chronic asthma, silicosis, asbestos induced pulmonary or pleural fibrosis, acute lung injury and acute respiratory distress (including bacterial pneumonia induced, trauma induced, viral pneumonia induced, ventilator induced, non-pulmonary sepsis induced, and aspiration induced).

Kidney Fibrosis

In some embodiments, the compositions and methods described herein can treat or slow down the progression of or prevent kidney fibrosis. Kidney fibrosis may develop as a result of chronic infection, obstruction of the ureter by calculi, malignant hypertension, radiation therapy, transplant rejection, severe diabetic conditions, or chronic exposure to heavy metals. In addition, idiopathic glomerulosclerosis and renal interstitial fibrosis have been reported in children and adults. Kidney fibrosis correlates well with the overall loss of renal function. Studies have shown that oral pirfenidone provides protective effect against heavy metal challenge and fibrosis reversal following diabetic challenge in rats.

Additionally, the antifibrotic action of pirfenidone in renal fibrosis following partial nephrectomy in rats has also been shown. Moreover, clinical studies administering oral pirfenidone have shown slowed renal function decline in focal segmental glomerulosclerosis patients. In some embodiments, because the kidneys vasculature is immediately downstream of the lung, inhaled delivery of pirfenidone or pyridone analog may be an effective means to prevent, manage or treat kidney fibrosis resulting from various medical conditions or procedures without exposing the systemic compartment to otherwise toxic drug levels associated with oral administration.

The term “kidney fibrosis” by non-limiting example relates to remodeling associated with or resulting chronic infection, obstruction of the ureter by calculi, malignant hypertension, radiation therapy, transplant rejection, severe diabetic conditions or chronic exposure to heavy metals. In some embodiments, kidney fibrosis correlates well with the overall loss of renal function.

Heart and Kidney Toxicity

In some embodiments, the compositions and methods described herein can treat or slow down the progression of or prevent heart and/or kidney toxicity. Chemotherapeutic agents have toxic effects upon multiple organ during therapy. By non-limiting example doxorubicin has a broad spectrum of therapeutic activity against various tumors. However, its

02 May 2016
2012212269

clinical use is limited by its undesirable systemic toxicity, especially in the heart and kidney. Treatment with pirfenidone reduced the severity of doxorubicin-induced toxicity as assessed by reduced mortality, diminished volume of recovered fluid in the abdominal cavity, and severity of cardiac and renal lesions at both the biochemical and morphological levels. In some embodiments, because the heart and kidney vasculature are immediately downstream of the lung, inhaled delivery of pirfenidone or pyridone analog may be an effective means to prevent, manage or treat chemotherapy-induced cardiac and/or renal inflammation without exposing the systemic compartment to otherwise toxic drug levels associated with oral administration. In some embodiments, inhaled delivery of pirfenidone or pyridone analog compound is used in the treatment of heart toxicity and/or kidney toxicity associated with chemotherapy or other therapeutic agents in a human.

The term “heart toxicity” by non-limiting example may be associated with or caused by exposure to chemotherapeutic agents having toxic effects. By non-limiting example doxorubicin has a broad spectrum of therapeutic activity against various tumors. However, its clinical use is limited by its undesirable systemic toxicity, especially in the heart and kidney.

The term “kidney toxicity” by non-limiting example may be associated with or caused by exposure to chemotherapeutic agents having toxic effects. By non-limiting example doxorubicin has a broad spectrum of therapeutic activity against various tumors. However, its clinical use is limited by its undesirable systemic toxicity, especially in the heart and kidney.

Cardiac Fibrosis

In some embodiments, the compositions and methods described herein can treat or slow down the progression of or prevent cardiac fibrosis. Cardiac remodeling as in chronic hypertension involves myocyte hypertrophy as well as fibrosis, an increased and non-uniform deposition of extracellular matrix proteins. The extracellular matrix connects myocytes, aligns contractile elements, prevents overextending and disruption of myocytes, transmits force and provides tensile strength to prevent rupture. Fibrosis occurs in many models of hypertension leading to an increased diastolic stiffness, a reduction in cardiac function and an increased risk of arrhythmias. If fibrosis rather than myocyte hypertrophy is the critical factor in impaired cardiovascular function, then reversal of cardiac fibrosis by itself may return cardiac function towards normal. Since collagen deposition is a dynamic process, appropriate

02 May 2016
2012212269

pharmacological intervention could selectively reverse existing fibrosis and prevent further fibrosis and thereby improve function, even if the increased systolic blood pressure was unchanged.

5 Treatment of DOCA-salt hypertensive rats with pirfenidone reversed and prevented fibrosis. Suggesting that pirfenidone or pyridone analog therapy may be an effective means to attenuate cardiac fibrosis associated with chronic hypertension and also the functional impairment of the heart in hypertensive humans. Moreover, the reversal of fibrosis following pirfenidone treatment of streptozotocin-diabetic rats was also shown (Miric et al., 2001). Together, and because the heart vasculature are immediately downstream of the lung, inhaled
10 delivery of pirfenidone or pyridone analog may be an effective means to prevent, manage or treat cardiac fibrosis resulting from various medical conditions or procedures, including by non-limiting example viral or bacterial infection, surgery, Duchenne muscular dystrophy, radiation, chemotherapy, and transplant rejection.

The term “cardiac fibrosis” by non-limiting example relates to remodeling associated
15 with or resulting from viral or bacterial infection, surgery, Duchenne muscular dystrophy, radiation therapy, chemotherapy, transplant rejection and chronic hypertension where myocyte hypertrophy as well as fibrosis is involved and an increased and non-uniform deposition of extracellular matrix proteins occurs. Fibrosis occurs in many models of hypertension leading to an increased diastolic stiffness, a reduction in cardiac function, an
20 increased risk of arrhythmias and impaired cardiovascular function.

Hepatic Fibrosis

In some embodiments, the compositions and methods described herein can treat or slow down the progression of or prevent hepatic fibrosis. Hepatic fibrosis occurs
consequence of severe liver damage in patients with chronic liver disease, caused by non-
25 limiting example persistent viral hepatitis, alcohol overload and autoimmune. Hepatic fibrosis involves an abnormal accumulation of extracellular matrix components, particularly collagens. Hepatic stellate cells are non-parenchymal liver cells residing in the perisinusoidal space. These cells have been shown to be the major cellular source of extracellular matrix in hepatic fibrosis. Studies have shown that oral pirfenidone provides protective effect against
30 dimethylnitrosamine-induced hepatic fibrosis in preventing weight loss, suppressed loss in liver weight, suppressed induction of hepatic fibrosis determined by histological evaluation

02 May 2016
2012212269

and reduced hepatic hydroxyproline levels. Expression of mRNA for type I collagen and transforming growth factor-beta in the liver were also suppressed by pirfenidone treatment. Additionally, clinical studies administering oral pirfenidone have shown decreased fibrosis and improved quality of life in Hepatitis C viral-related liver disease patients. Together, and because the liver vasculature is downstream of the lung, these results suggest that inhaled delivery of pirfenidone or pyridone analog may be an effective means to prevent, manage or treat hepatic fibrosis resulting from various medical conditions or procedures without exposing the systemic compartment to otherwise toxic drug levels associated with oral administration.

The term “hepatic fibrosis” by non-limiting example may be associated with or caused by severe liver damage in patients with chronic liver disease, caused by non-limiting example persistent viral hepatitis, alcohol overload and autoimmune diseases. Hepatic fibrosis involves an abnormal accumulation of extracellular matrix components, particularly collagens. Hepatic stellate cells are non-parenchymal liver cells residing in the perisinusoidal space.

Multiple Sclerosis

In some embodiments, the compositions and methods described herein can treat or slow down the progression of or prevent multiple sclerosis. Multiple sclerosis is a demyelinating disorder that is characterized by neurological deficits attributable to demyelinating lesions and progressive axonal loss in the white matter. The evidence that TNF-alpha plays a pivotal role in the pathogenesis of multiple sclerosis led to evaluation of pirfenidone in this indication. In a clinical study, oral pirfenidone improved the Scripps Neurological Rating Scale scores over placebo. Further, pirfenidone reduced the incidence of relapses and was associated with a marked improvement in bladder dysfunction. Together, and because the central nervous system vasculature is immediately downstream of the lung, these results suggest that inhaled delivery of pirfenidone or pyridone analog may be an effective means to prevent, manage or treat multiple sclerosis without exposing the systemic compartment to otherwise toxic drug levels associated with oral administration.

The term “multiple sclerosis” is a demyelinating disorder that is characterized by neurological deficits attributable to demyelinating lesions and progressive axonal loss in the white matter.

02 May 2016
2012212269**Chronic Obstructive Pulmonary Disease (COPD)**

In some embodiments, the compositions and methods described herein can treat or slow down the progression of or prevent COPD. Oxidants and oxidative stress due to, by non-limiting example, cigarette smoking promote lung inflammation, which is mediated, at least in part, by activation of the transcription factors nuclear factor (NF)- κ B and activator protein (AP)-1. These coordinate the expression of several genes thought to be important in COPD, such as interleukin (IL)-8 and TNF α . These pro-inflammatory cytokines and chemokines, together with IL-1 β , strongly activate the p38 subgroup of mitogen-activated protein kinases (MAPKs), a family of signal transduction enzymes that also include extracellular signal-regulated kinases (ERK) and c-jun NH2-terminal kinases (JNK). JNK and p38 members are activated mainly by cytokines implicated in inflammation and apoptosis. Within the MAPK family, both the JNK and the p38 subgroups are involved in mediating pro-inflammatory responses, though p38 seems to play a prominent role in COPD. Pirfenidone has been shown to inhibit both TNF-alpha and p38-gamma MAPK. Moreover, silencing p38-gamma MAPK has been demonstrated to have potential to restore COPD sensitivity to corticosteroids (Mercado et al., 2007). In some embodiments, inhaled delivery of pirfenidone or pyridone analog compound is used in the treatment of COPD in a human. In some embodiments, inhaled delivery of pirfenidone or pyridone analog may be an effective means to prevent, manage or treat COPD or associated illness without exposing the systemic compartment to otherwise toxic drug levels associated with oral administration. Moreover, inhaled delivery of pirfenidone or pyridone analog may serve as conjunctive therapy with corticosteroids to restore their usefulness in this indication.

The term “chronic obstructive pulmonary disease” or “COPD” by non-limiting example may be associated with or caused by exposure to tobacco smoke and preexisting asthma. COPD describes a wide range of airway disorders that range from simple chronic bronchitis (smokers cough) to the more severe chronic obstructive bronchitis. The addition of episodes of airway hyper-reactivity to the above syndrome establishes the diagnosis of chronic asthmatic bronchitis. Chronic obstructive pulmonary disease includes, but is not limited to, chronic bronchitis, emphysema, and/or pulmonary hypertension.

02 May 2016
2012212269**Asthma**

In some embodiments, the compositions and methods described herein can treat or slow down the progression of or prevent asthma. TNF-alpha has been shown to be a highly pro-inflammatory cytokine in asthma, as it upregulates adhesion molecules, increases mucin secretion, and promotes airway remodeling. TNF-alpha is produced by a large number of cells in the airways, including mast cells, smooth muscle cells, epithelial cells, monocytes, and macrophages. This cytokine has been shown to be relevant and increased in patients with asthma. Clinical studies using anti-TNF-alpha therapy have produced encouraging results. In one set of studies using a soluble form of recombinant human TNF-alpha receptor (etanercept) the medication improved FEV1 and improved quality of life. Another clinical study administering an anti-TNF-alpha antibody reduced asthma exacerbation (infliximab). However, because of concerns associated with adverse events future investigation of these therapies in asthma is unlikely. Because pirfenidone has been shown to inhibit TNF-alpha, inhaled delivery of pirfenidone or pyridone analog may be an effective means to manage or treat asthma or associated illness without exposing the systemic compartment to otherwise toxic drug levels associated with oral administration. In some embodiments, inhaled delivery of pirfenidone or pyridone analog compound is used in the treatment of asthma in a human. Moreover, inhaled delivery of pirfenidone or pyridone analog may serve as conjunctive therapy with corticosteroids to restore their usefulness in asthma patients exhibiting steroid resistance.

The term "asthma" is associated with or caused by environmental and genetic factors. Asthma is a common chronic inflammatory disease of the airways characterized by variable and recurring symptoms, reversible airflow obstruction, and bronchospasm. Symptoms include wheezing, coughing, chest tightness, and shortness of breath. The term asthma may be used with one or more adjectives to indicate cause. Non-limiting examples of asthma include, but are not limited to, allergic asthma, non-allergic asthma, acute severe asthma, chronic asthma, clinical asthma, nocturnal asthma, allergen-induced asthma, aspirin-sensitive asthma, exercise-induced asthma, child-onset asthma, adult-onset asthma, cough-variant asthma, occupational asthma, steroid-resistant asthma, or seasonal asthma.

02 May 2016
2012212269**Lung Inflammation**

In some embodiments, the compositions and methods described herein can treat or slow down the progression of or prevent lung inflammation. Pirfenidone therapy has shown to have anti-inflammatory effects in addition to anti-fibrotic effects. In some embodiments, pirfenidone or pyridone analog compound is administered to a human to treat lung inflammation. Lung inflammation is associated with or contributes to the symptoms of bronchitis, asthma, lung fibrosis, chronic obstructive pulmonary disorder (COPD), and pneumonitis.

Glaucoma Surgery Post-Operative Fibrosis

The success of glaucoma filtration surgery is dependent on the degree of post-operative wound healing and the amount of scar tissue formation. Bleb failure occurs as fibroblasts proliferate and migrate toward the wound, eventually causing scarring and closure of the fistula tract. This frequently leads to poor postoperative intraocular pressure control with subsequent progressive optic nerve damage. The use of adjunctive antifibrotic agents such as 5-fluorouracil and mitomycin C has significantly improved the success rate of filtration surgery. However, because of their nonspecific mechanisms of action, these agents can cause widespread cell death and apoptosis, resulting in potentially sight-threatening complications such as severe postoperative hypotony, bleb leaks, and endophthalmitis. Thus, alternative antifibrotic agents are needed. For this purpose, the anti-fibrotic agent pirfenidone or pyridone analog may prove beneficial.

The present invention provides, in several embodiments as herein disclosed, compositions and methods for pirfenidone and pyridone analog compound formulations that offer unprecedented advantages with respect to localized delivery of pirfenidone or pyridone analog in a manner that permits both rapid and sustained availability of therapeutically useful pirfenidone or pyridone analog levels to one or more desired tissues.

In certain preferred embodiments, and as described in greater detail below, delivery of the pirfenidone or pyridone analog compound formulation is to the respiratory tract tissues in mammalian subjects, for example, via the respiratory airways to middle airways and/or pulmonary beds (*e.g.*, alveolar capillary beds) in human patients. According to certain particularly preferred embodiments, delivery to these regions of the lung may be achieved by

02 May 2016
2012212269

inhalation therapy of a pirfenidone or pyridone analog compound formulation as described herein.

These and related embodiments will usefully provide therapeutic and/or prophylactic benefit, by making therapeutically effective pirfenidone or pyridone analog available to a
5 desired tissue promptly upon administration, while with the same administration event also offering time periods of surprisingly sustained duration during which locally delivered pirfenidone or pyridone analog is available for a prolonged therapeutic effect.

The compositions and methods disclosed herein provide for such rapid and sustained localized delivery of a pirfenidone or pirfenidone or pyridone analog pyridone analog
10 compound to a wide variety of tissues. Contemplated are embodiments for the treatment of numerous clinically significant conditions including pulmonary fibrosis, chronic obstructive pulmonary disease (COPD), asthma, cystic fibrosis, cardiac fibrosis, transplantation (*e.g.*, lung, liver, kidney, heart, etc.), vascular grafts, and/or other conditions such as multiple sclerosis for which rapid and sustained bioavailable pirfenidone or pyridone analog therapy
15 may be indicated.

Various embodiments thus provide compositions and methods for optimal prophylactic and therapeutic activity in prevention and treatment of pulmonary fibrosis in human and/or veterinary subjects using aerosol administration, and through the delivery of high-concentration (or dry formulation), sustained-release active drug exposure directly to the
20 affected tissue. Specifically, and in certain preferred embodiments, concentrated doses are delivered of a pirfenidone or pyridone analog.

Without wishing to be bound by theory, according to certain of these and related embodiments as described in greater detail herein, a pirfenidone or pyridone analog is provided in a formulation having components that are selected to deliver an efficacious dose
25 of pirfenidone or pyridone analog following aerosolization of a liquid, dry powder or metered-dose formulation providing rapid and sustained localized delivery of pirfenidone or pyridone analog to the site of desired effect.

According to certain related embodiments, regulation of the total amount of dissolved solutes in a pirfenidone or pyridone analog compound formulation is believed, according to
30 non-limiting theory, to result in aqueous pirfenidone or pyridone analog compound formulations having therapeutically beneficial properties, including the properties of

02 May 2016

2012212269

nebulized liquid particles formed from aqueous solutions of such formulations. Additionally, and as disclosed herein, it has been discovered that within the parameters provided herein as pertain to pirfenidone or pyridone analog compound concentration, pH, and total solute concentration, tolerability of formulations at or near the upper portion of the total solute concentration range can be increased by inclusion of a taste-masking agent as provided herein.

An unexpected observation is that exposure of inhaled pirfenidone to the lung surface results in depletion of essential lung-surface cations and increased propensity for acute toxicity. The apparent mechanism for this depletion is pirfenidone's ability to chelate ions such as iron(III) in a ratio of three pirfenidone molecules per on iron(III) ion. Chelation of iron(III) occurs at about one-half the chelation strength of EDTA. One method to prevent lung-surface ion depletion is to formulation prifenidone with a multivalent ion. By non-limiting example, such multi-valent cations may include iron(II), iron(III), calcium, magnesium, etc. By non-limiting example, formulation of pirfenidone was found to chlate magnesium at a ratio of two pirfenidone molecules to one magnesium ion. Thus, formulation of between about two and ten pirfenidone molecules with one magnesium molecule results in filling or saturating the chelation capacity of prifenidone and reduces pirfenidone's to deplete lung-surface cations. Coupling this solution with the need to adjust formulation osmolality and permeant ion content, the salt form of multivalent ion may also be beneficial. By non-limiting example, using magnesium chloride to formulate pirfenidone reduces pirfenidone's ability to deplete essential lung-surface cations, contributes to adjusting the formulations osmolality and serves to provide the formulation a chloride permeant ion. In certain such embodiments, for example, a pirfenidone or pyridone analog compound formulation that comprises pirfenidone or a pyridone analog alone or formulated with excipients dissolved in a simple aqueous solution that may be aerosolized and injected or inhaled to the nasal or pulmonary compartment. Such a formulation may contain a multivalent cation and/or be buffered to a pH from about 4.0 to about 11.0, more preferably from about pH 4.0 to about pH 8.0, at a concentration of at least 34 mcg/mL to about 463 mg/mL, and having a total osmolality at least 100 mOsmol/kg to about 6000 mOsmol/kg, or 300 to about 5000 mOsmol/kg. Such a simple aqueous formulation may further comprise a taste-masking agent thereby to become tolerable for inhalation administration (*i.e.*, to overcome undesirable taste

02 May 2016
2012212269

or irritative properties that would otherwise preclude effective therapeutic administration). Hence and as described in greater detail herein, regulation of formulation conditions with respect to pH, buffer type, pirfenidone or pyridone analog concentration, total osmolality and potential taste-masking agent, provides certain therapeutic and other advantages.

5 In certain such embodiments, for example, a pirfenidone or pyridone analog compound formulation that comprises pirfenidone or a pyridone analog in a dry powder formulation alone or formulated with an excipient, such as a multivalent cation providing improved stability and/or dispersion properties, such that at least 0.1 mg to about 100 mg may be dispersed and injected or inhaled to the nasal or pulmonary compartment. Hence and
10 as described in greater detail herein, regulation of formulation conditions with respect to dispersion excipient, pirfenidone or pyridone analog stability (including, by non-limiting example polymorph, amorphous content and water content), pirfenidone or pyridone analog amount and potential taste-masking agent, provides certain therapeutic and other advantages.

In certain such embodiments, for example, a pirfenidone or pyridone analog
15 compound formulation that comprises pirfenidone or a pyridone analog in a pressurized meter-dose inhaler configuration providing improved stability and/or aerosol properties, such that at least 0.1 mg to about 100 mg may be aerosolized and injected or inhaled to the nasal or pulmonary compartment. Hence and as described in greater detail herein, regulation of formulation conditions with respect to propellant, suitable pressurized metered-dose inhaler
20 canister, pirfenidone or pyridone analog stability provides certain therapeutic and other advantages.

In certain preferred embodiments, a pirfenidone or pyridone analog compound formulation or salts thereof may serve as prodrugs, sustained-release or active substances in the presently disclosed formulations and compositions and may be delivered, under
25 conditions and for a time sufficient to produce maximum concentrations of sustained-release or active drug to the respiratory tract (including pulmonary beds, nasal and sinus cavities), and other non-oral topical compartments including, but not limited to the skin, rectum, vagina, urethra, urinary bladder, eye, and ear. As disclosed herein, certain particularly preferred embodiments relate to administration, via oral and/or nasal inhalation, of a
30 pirfenidone or pyridone analog compound to the lower respiratory tract, in other words, to the lungs or pulmonary compartment (*e.g.*, respiratory bronchioles, alveolar ducts, and/or

02 May 2016

2012212269

alveoli), as may be effected by such “pulmonary delivery” to provide effective amounts of the pirfenidone or pyridone analog compound to the pulmonary compartment and/or to other tissues and organs as may be reached via the circulatory system subsequent to such pulmonary delivery of the pirfenidone or pyridone analog compound to the pulmonary vasculature.

Because different drug products are known to have varying efficacies depending on the dose, form, concentration and delivery profile, certain presently disclosed embodiments provide specific formulation and delivery parameters that produce anti-inflammatory, anti-fibrotic, anti-demyelination and/or tissue-remodeling results that are prophylactic or therapeutically significant. These and related embodiments thus preferably include a pirfenidone or pyridone analog compound such as pirfenidone or pyridone analog alone or a salt thereof. As noted above, however, the invention is not intended to be so limited and may relate, according to particularly preferred embodiments, to pirfenidone or a salt thereof. Other contemplated embodiments may relate to another pyridone analog compound such as those disclosed herein.

As a non-limiting example, in a preferred embodiment, a pyridone analog compound as provided herein (*e.g.*, pirfenidone) formulated to permit mist, gas-liquid suspension or liquid nebulized, dry powder and/or metered-dose inhaled aerosol administration to supply effective concentrations or amounts conferring desired anti-inflammatory, anti-fibrotic or tissue-remodeling benefits, for instance, to prevent, manage or treat patients with pulmonary fibrosis.

Because different drug products are known to vary in efficacy depending on the dose, form, concentration and delivery profile, the presently disclosed embodiments provide specific formulation and delivery parameters that produce protection against and treatment for pulmonary fibrosis associated, by non-limiting example with infection, radiation therapy, chemotherapy, inhalation of environmental pollutants (*e.g.* dust, vapors, fumes, and inorganic and organic fibers), hypersensitivities, silicosis, byssinosis, genetic factors and transplant rejection.

These and related applications are also contemplated for use in the diseased lung, sinus, nasal cavity, heart, kidney, liver, nervous system and associated vasculature. The pirfenidone or pyridone analog compound formulations and methods described herein may be

02 May 2016
2012212269

used with commercially available inhalation devices, or with other devices for aerosol therapeutic product administration.

As a non-limiting example, in a preferred embodiment, a pyridone analog compound as provided herein (*e.g.*, pirfenidone) formulated to permit mist, gas-liquid suspension or liquid nebulized, dry powder and/or metered-dose inhaled aerosol administration to supply effective concentrations or amounts conferring desired anti-inflammatory, anti-fibrotic or tissue-remodeling benefits, for instance, to prevent, manage or treat cardiac fibrosis in human and/or veterinary subjects. Such embodiments provide for direct and high concentration delivery of the pirfenidone or pyridone analog compound to the pulmonary vasculature immediately upstream of the left atrium and hence, to the coronary arterial system with interluminal atrial and ventricular exposure.

Because different drug products are known to vary in efficacy depending on the dose, form, concentration and delivery profile, the presently disclosed embodiments provide specific formulation and delivery parameters that produce protection against and treatment for cardiac fibrosis associated, by non-limiting example with infection, surgery, radiation therapy, chemotherapy and transplant rejection.

As a non-limiting example, in a preferred embodiment, a pyridone analog compound as provided herein (*e.g.*, pirfenidone) formulated to permit mist, gas-liquid suspension or liquid nebulized, dry powder and/or metered-dose inhaled aerosol administration to supply effective concentrations or amounts conferring desired anti-inflammatory, anti-fibrotic or tissue-remodeling benefits, for instance, to prevent, manage or treat kidney fibrosis. Such embodiments provide for direct and high concentration delivery of the pirfenidone or pyridone analog compound to the pulmonary vasculature immediately upstream of the left atrium, left ventricle and hence, to the kidney vasculature.

Because different drug products are known to vary in efficacy depending on the dose, form, concentration and delivery profile, the presently disclosed embodiments provide specific formulation and delivery parameters that produce protection against and treatment for kidney fibrosis associated, by non-limiting example with infection, ureter calculi, malignant hypertension, radiation therapy, diabetes, exposure to heavy metals, chemotherapy and transplant rejection.

02 May 2016
2012212269

As a non-limiting example, in a preferred embodiment, a pyridone analog compound as provided herein (*e.g.*, pirfenidone) formulated to permit mist, gas-liquid suspension or liquid nebulized, dry powder and/or metered-dose inhaled aerosol administration to supply effective concentrations or amounts conferring desired anti-inflammatory benefits, for instance, to prevent, manage or treat heart or kidney toxicity. Such embodiments provide for direct and high concentration delivery of the pirfenidone or pyridone analog compound to the pulmonary vasculature immediately upstream of the left atrium, left ventricle, and hence, to the heart and kidney vasculature.

Because different drug products are known to vary in efficacy depending on the dose, form, concentration and delivery profile, the presently disclosed embodiments provide specific formulation and delivery parameters that produce protection against and treatment for heart or kidney toxicity associated, by non-limiting example with chemotherapy.

As a non-limiting example, in a preferred embodiment, a pyridone analog compound as provided herein (*e.g.*, pirfenidone) formulated to permit mist, gas-liquid suspension or liquid nebulized, dry powder and/or metered-dose inhaled aerosol administration to supply effective concentrations or amounts conferring desired anti-inflammatory, anti-fibrotic or tissue-remodeling benefits, for instance, to prevent, manage or treat hepatic fibrosis. Such embodiments provide for direct and high concentration delivery of the pirfenidone or pyridone analog compound to the pulmonary vasculature immediately upstream of the left atrium, left ventricle and hence, to the hepatic vasculature.

Because different drug products are known to vary in efficacy depending on the dose, form, concentration and delivery profile, the presently disclosed embodiments provide specific formulation and delivery parameters that produce protection against and treatment for hepatic fibrosis associated, by non-limiting example with hepatic infection, hepatitis, alcohol overload, autoimmune disease, radiation therapy, chemotherapy and transplant rejection.

As a non-limiting example, in a preferred embodiment, a pyridone analog compound as provided herein (*e.g.*, pirfenidone) formulated to permit mist, gas-liquid suspension or liquid nebulized, dry powder and/or metered-dose nasal-injected or inhaled, or orally-inhaled aerosol administration to supply effective concentrations or amounts conferring desired anti-inflammatory and/or anti-demyelination benefits, for instance, to prevent, manage or treat

02 May 2016

2012212269

multiple sclerosis. If by oral inhalation, such embodiments provide for direct and high concentration delivery of the pirfenidone or pyridone analog compound to the pulmonary vasculature immediately upstream of the left atrium, left ventricle and hence, to the central nervous system. If by nasal injection or nasal inhalation, such embodiments provide for

5 direct and high concentration delivery of the pirfenidone or pyridone analog compound to the nasal and sinus vasculature immediately upstream of the central nervous system.

Because different drug products are known to vary in efficacy depending on the dose, form, concentration and delivery profile, the presently disclosed embodiments provide specific formulation and delivery parameters that produce protection against and treatment

10 for multiple sclerosis associated.

As a non-limiting example, in a preferred embodiment, a pyridone analog compound as provided herein (*e.g.*, pirfenidone) formulated to permit mist, gas-liquid suspension or liquid nebulized, dry powder and/or metered-dose inhaled aerosol administration to supply effective concentrations or amounts conferring desired anti-inflammatory, anti-fibrotic or

15 tissue-remodeling benefits, for instance, to prevent, manage or treat patients with diseases associated with chronic obstructive pulmonary disease (COPD), including emphysema and chronic bronchitis.

Because different drug products are known to vary in efficacy depending on the dose, form, concentration and delivery profile, the presently disclosed embodiments provide

20 specific formulation and delivery parameters that produce protection against and treatment for COPD associated, by non-limiting example with exposure to pipe, cigar and cigarette smoke, secondhand smoke, air pollution, and chemical fumes or dust, and/or alpha-1 antitrypsin deficiency.

As a non-limiting example, in a preferred embodiment, a pyridone analog compound as provided herein (*e.g.*, pirfenidone) formulated to permit mist, gas-liquid suspension or liquid nebulized, dry powder and/or metered-dose inhaled aerosol administration to supply effective concentrations or amounts conferring desired anti-inflammatory benefits, for

25 instance, to prevent, manage or treat patients with asthma.

Because different drug products are known to vary in efficacy depending on the dose, form, concentration and delivery profile, the presently disclosed embodiments provide

30 specific formulation and delivery parameters that produce protection against and treatment

02 May 2016
2012212269

for asthma associated, by non-limiting example with exercise, genetics, airborne allergens, inhaled irritants such as pipe, cigar and cigarette smoke, and childhood respiratory infection.

As a non-limiting example, in a preferred embodiment, a pyridone analog compound as provided herein (*e.g.*, pirfenidone) formulated to permit mist, gas-liquid suspension or liquid nebulized, dry powder and/or metered-dose inhaled aerosol administration to supply effective concentrations or amounts conferring desired anti-fibrotic, anti-inflammatory or tissue-remodeling benefits, for instance, to prevent, manage or treat patients with cystic fibrosis. Such embodiments may include co-formulation or co-administration of a pyridone analog compound with an antibiotic, steroid, hyperosmolar solution, DNase or other mucus thinning agent, or other agent.

Because different drug products are known to vary in efficacy depending on the dose, form, concentration and delivery profile, the presently disclosed embodiments provide specific formulation and delivery parameters that produce protection against and treatment for cystic fibrosis.

For the applications described herein, liquid nebulized, dry powder or metered-dose aerosol pirfenidone or pyridone analog compound (or salt thereof) may be co-administered, administered sequentially or prepared in a fixed combination with an antimicrobial (*e.g.* tobramycin and/or other aminoglycoside such as amikacin, aztreonam and/or other beta or mono-bactam, ciprofloxacin, levofloxacin and/or other, fluoroquinolones, azithromycin and/or other macrolides or ketolides, tetracycline and/or other tetracyclines, quinupristin and/or other streptogramins, linezolid and/or other oxazolidinones, vancomycin and/or other glycopeptides, and chloramphenicol and/or other phenicols, and colistin and/or other polymyxins), bronchodilator (*e.g.* beta-2 agonists and muscarinic antagonists), corticosteroids (*e.g.* salmeterol, fluticasone and budesonide), glucocorticoids (*e.g.* prednisone), Cromolyn, Nedocromil, Leukotriene modifiers (*e.g.* montelukast, zafirlukast and zileuton) hyperosmolar solution, DNase or other mucus thinning agent, interferon gamma, cyclophosphamide, colchicine, N-acetylcysteine, azathioprine, bromhexine, endothelin receptor antagonist (*e.g.* bosentan and ambrisentan), PDE5 inhibitor (*e.g.* sildenafil, vardenafil and tadalafil), PDE4 inhibitor (*e.g.* roflumilast, cilomilast, oglemilast, tetomilast and SB256066), prostinoid (*e.g.* epoprostenol, iloprost and treprostinin), nitric oxide or nitric oxide-donating compound, IL-13 blocker, IL-10 blocker, CTGF-specific antibody, CCN2 inhibitors, angiotensin-converting

02 May 2016
2012212269

enzyme inhibitors, angiotensin receptor antagonists, PDGF inhibitors, PPAR antagonist, imatinib, CCL2-specific antibody, CXCR2 antagonist, triple growth factor kinase inhibitor, anticoagulant, TNF blocker, tetracycline or tetracycline derivative, 5-lipoxygenase inhibitor, pituitary hormone inhibitor, TGF-beta-neutralizing antibody, copper chelator, angiotensin II

5 receptor antagonist, chemokine inhibitor, NF-kappaB inhibitor, NF-kappaB antisense oligonucleotide, IKK-1 and -2 inhibitor (e.g. imidazoquinoxaline or derivative, and quinazoline or derivative), JNK2 and/or p38 MAPK inhibitor (e.g. pyridylimidazolbutyn-I-ol, SB856553, SB681323, diaryl urea or derivative, and indole-5-carboxamide), PI3K inhibitor, LTB4 inhibitor, antioxidant (e.g. Mn-pentaazatetracyclohexacosatriene, M40419, N-acetyl-L-

10 cysteine, Mucomyst, Fluimucil, Nacystelyn, Erdosteine, Ebeselen, thioredoxin, glutathione peroxidase memetrics, Curcumin C3 complex, Resveratrol and analogs, Tempol, catalytic antioxidants, and OxSODrol), TNF scavenger (e.g. infliximab, ethercept, adalumimab, PEG-sTNFR 1, afelimomab, and antisense TNF-alpha oligonucleotide), Interferon beta-1a (Avonex, Betaseron, or Rebif), glatiramer acetate (Copaxone), mitoxantrone (Novantrone),

15 natalizumab (Tysabri), Methotrexate, azathioprine (Imuran), intravenous immunoglobulin (IVIg), cyclophosphamide (Cytosan), lioresal (Baclofen), tizanidine (Zanaflex), benzodiazepine, cholinergic medications, antidepressants and amantadine.

As shown as a promising approach to treat cancer and pulmonary arterial hypertension, to enable “cocktail therapy” or “cocktail prophylaxis” in fibrotic disease, more

20 specifically idiopathic pulmonary fibrosis and other pulmonary fibrotic disease, methods to administer pirfenidone or pyridone analog as either co-administered, administered sequentially, or co-prescribed (such that medicines are requested by a prescribing physician to be taken in some sequence as combination therapy to treat the same disease) with agents targeting fibrotic or inflammatory disease. By non-limiting example, pirfenidone or pyridone

25 analog is administered either in fixed combination, co-administered, administered sequentially, or co-prescribed with the monoclonal GS-6624 (formerly known as AB0024), analog or another antibody targeting LOXL2 protein associated with connective tissue biogenesis to reduce inflammation and/or fibrosis. By another non-limiting example, pirfenidone or pyridone analog is administered either in fixed combination, co-administered,

30 administered sequentially, or co-prescribed with IW001 (Type V collagen), analog or other collagen targeting immunogenic tolerance to reduce inflammation and/or fibrosis. By

02 May 2016
2012212269

another non-limiting example, pirfenidone or pyridone analog is administered either in fixed combination, co-administered, administered sequentially, or co-prescribed with PRM-151 (recombinant pentraxin-2), analog or other molecule targeting regulation of the injury response to reduce inflammation and/or fibrosis. By another non-limiting example,

5 pirfenidone or pyridone analog is administered either in fixed combination, co-administered, administered sequentially, or co-prescribed with CC-903 (Jun kinase inhibitor), analog or other Jun kinase inhibitor to reduce the inflammatory response. By another non-limiting example, pirfenidone or pyridone analog is administered either in fixed combination, co-

administered, administered sequentially, or co-prescribed with STX-100 (monoclonal

10 antibody targeting integrin alpha-v beta-6), analog or other antibody targeting integrin alpha-v beta-6 or other integrin to reduce fibrosis. By another non-limiting example, pirfenidone or pyridone analog is administered either in fixed combination, co-administered, administered sequentially, or co-prescribed with QAX576 (monoclonal antibody targeting interleukin 13 [IL-13]), analog or other antibody targeting IL-13 to reduce inflammation. By another non-

limiting example, pirfenidone or pyridone analog is administered either in fixed combination, co-administered, administered sequentially, or co-prescribed with FG-3019 (monoclonal antibody targeting connective tissue growth factor [CTGF]), analog or other antibody targeting CTGF to reduce fibrosis. By another non-limiting example, pirfenidone or pyridone analog is administered either in fixed combination, co-administered, administered sequentially, or co-prescribed with CNTO-888 (a monoclonal antibody targeting chemokine [C-C motif] ligand 2 [CCL2]), analog or other antibody targeting CCL2 to reduce fibrosis. By another non-limiting example, pirfenidone or pyridone analog is administered either in fixed combination, co-administered, administered sequentially, or co-prescribed with Esbriet, Pirespa or Pirfenex (trade names for pirfenidone), or analog targeting inflammation and

15 limiting example, pirfenidone or pyridone analog is administered either in fixed combination, co-administered, administered sequentially, or co-prescribed with FG-3019 (monoclonal antibody targeting connective tissue growth factor [CTGF]), analog or other antibody targeting CTGF to reduce fibrosis. By another non-limiting example, pirfenidone or pyridone analog is administered either in fixed combination, co-administered, administered sequentially, or co-prescribed with CNTO-888 (a monoclonal antibody targeting chemokine [C-C motif] ligand 2 [CCL2]), analog or other antibody targeting CCL2 to reduce fibrosis. By another non-limiting example, pirfenidone or pyridone analog is administered either in fixed combination, co-administered, administered sequentially, or co-prescribed with Esbriet, Pirespa or Pirfenex (trade names for pirfenidone), or analog targeting inflammation and

20 sequentially, or co-prescribed with CNTO-888 (a monoclonal antibody targeting chemokine [C-C motif] ligand 2 [CCL2]), analog or other antibody targeting CCL2 to reduce fibrosis. By another non-limiting example, pirfenidone or pyridone analog is administered either in fixed combination, co-administered, administered sequentially, or co-prescribed with Esbriet, Pirespa or Pirfenex (trade names for pirfenidone), or analog targeting inflammation and

fibrosis. By another non-limiting example, pirfenidone or pyridone analog is administered either in fixed combination, co-administered, administered sequentially, or co-prescribed with BIBF-1120 (also known as Vargatef; a triple kinase inhibitor targeting vascular endothelial growth factor [VEGF], platelet-derived growth factor [PDGF] and fibroblast growth factor [FGF]), analog or other triple kinase inhibitor to reduce fibrosis and/or inflammation.

25 fibrosis. By another non-limiting example, pirfenidone or pyridone analog is administered either in fixed combination, co-administered, administered sequentially, or co-prescribed with BIBF-1120 (also known as Vargatef; a triple kinase inhibitor targeting vascular endothelial growth factor [VEGF], platelet-derived growth factor [PDGF] and fibroblast growth factor [FGF]), analog or other triple kinase inhibitor to reduce fibrosis and/or inflammation.

30 As with administration of pirfenidone, oral and parenteral routes of administration (by non-limiting example, intravenous and subcutaneous) of other compounds, molecules and

02 May 2016
2012212269

antibodies targeting the reduction of inflammation and/or fibrosis is often associated with, by non-limiting example, adverse reactions such as gastrointestinal side effects, liver, kidney, skin, cardiovascular or other toxicities. As described herein for pirfenidone or pyridone analogs, the benefits of oral or intranasal inhalation directly to the lung or tissues

5 immediately downstream of the nasal and/or pulmonary compartments will also benefit these compounds. Therefore, by non-limiting example, the monoclonal GS-6624 (formerly known as AB0024), analog or another antibody targeting LOXL2 protein associated with connective tissue biogenesis to reduce inflammation and/or fibrosis may be administered by oral or intranasal inhalation for direct delivery to the lung or tissues immediately downstream of the nasal or pulmonary compartments. By another non-limiting example, PRM-151

10 (recombinant pentraxin-2), analog or other molecule targeting regulation of the injury response to reduce inflammation and/or fibrosis may be administered by oral or intranasal inhalation for direct delivery to the lung or tissues immediately downstream of the nasal or pulmonary compartments. By another non-limiting example, CC-903 (Jun kinase inhibitor),

15 analog or other Jun kinase inhibitor to reduce the inflammatory response may be administered by oral or intranasal inhalation for direct delivery to the lung or tissues immediately downstream of the nasal or pulmonary compartments. By another non-limiting example, STX-100 (monoclonal antibody targeting integrin alpha-v beta-6), analog or other antibody targeting integrin alpha-v beta-6 or other integrin to reduce fibrosis may be

20 administered by oral or intranasal inhalation for direct delivery to the lung or tissues immediately downstream of the nasal or pulmonary compartments. By another non-limiting example, QAX576 (monoclonal antibody targeting interleukin 13 [IL-13]), analog or other antibody targeting IL-13 to reduce inflammation may be administered by oral or intranasal inhalation for direct delivery to the lung or tissues immediately downstream of the nasal or

25 pulmonary compartments. By another non-limiting example, FG-3019 (monoclonal antibody targeting connective tissue growth factor [CTGF]), analog or other antibody targeting CTGF to reduce fibrosis may be administered by oral or intranasal inhalation for direct delivery to the lung or tissues immediately downstream of the nasal or pulmonary compartments. By another non-limiting example, CNTO-888 (a monoclonal antibody targeting chemokine [C-C motif] ligand 2 [CCL2]), analog or other antibody targeting CCL2 to reduce fibrosis may be

30 administered by oral or intranasal inhalation for direct delivery to the lung or tissues

02 May 2016
2012212269

immediately downstream of the nasal or pulmonary compartments. By another non-limiting example, BIBF-1120 (also known as Vargatef; a triple kinase inhibitor targeting vascular endothelial growth factor [VEGF], platelet-derived growth factor [PDGF] and fibroblast growth factor [FGF]), analog or other triple kinase inhibitor to reduce fibrosis and/or inflammation may be administered by oral or intranasal inhalation for direct delivery to the lung or tissues immediately downstream of the nasal or pulmonary compartments.

Aerosol administration directly to one or more desired regions of the respiratory tract, which includes the upper respiratory tract (*e.g.*, nasal, sinus, and pharyngeal compartments), the respiratory airways (*e.g.*, laryngeal, tracheal, and bronchial compartments) and the lungs or pulmonary compartments (*e.g.*, respiratory bronchioles, alveolar ducts, alveoli), may be effected (*e.g.*, “pulmonary delivery”) in certain preferred embodiments through intra-nasal or oral inhalation to obtain high and titrated concentration of drug, pro-drug active or sustained-release delivery to a site of respiratory pathology. Aerosol administration such as by intra-nasal or oral inhalation may also be used to provide drug, pro-drug active or sustained-release delivery through the pulmonary vasculature (*e.g.*, further to pulmonary delivery) to reach other tissues or organs, by non-limiting example, the heart, brain, liver central nervous system and/or kidney, with decreased risk of extra-respiratory toxicity associated with non-respiratory routes of drug delivery. Accordingly, because the efficacy of a particular pyridone compound (*e.g.*, pirfenidone) therapeutic composition may vary depending on the formulation and delivery parameters, certain embodiments described herein reflect reformulations of compositions and novel delivery methods for recognized active drug compounds. Other embodiments contemplate topical pathologies and/or infections that may also benefit from the discoveries described herein, for example, through direct exposure of a pirfenidone or pyridone analog compound formulation as provided herein to diseased skin, rectum, vagina, urethra, urinary bladder, eye, and/or ear, including aerosol delivery to a burn wound to prevent scarring.

In addition to the clinical and pharmacological criteria according to which any composition intended for therapeutic administration (such as the herein described pirfenidone or pyridone analog compound formulations) may be characterized, those familiar with the art will be aware of a number of physicochemical factors unique to a given drug composition. These include, but are not limited to aqueous solubility, viscosity, partitioning coefficient

02 May 2016
2012212269

(LogP), predicted stability in various formulations, osmolality, surface tension, pH, pKa, pK_b, dissolution rate, sputum permeability, sputum binding/inactivation, taste, throat irritability and acute tolerability.

Other factors to consider when selecting the particular product form include physical chemistry of the formulation (*e.g.*, a pirfenidone or pyridone analog compound formulation), the intended disease indication(s) for which the formulation is to be used, clinical acceptance, and patient compliance. As non-limiting examples, a desired pirfenidone or pyridone analog compound formulation for aerosol delivery (*e.g.*, by oral and/or intra-nasal inhalation of a mist such as a nebulized suspension of liquid particles, a dispersion of a dry powder formulation or aerosol generated by meter-dose propellant), may be provided in the form of a simple liquid such as an aqueous liquid (*e.g.*, soluble pirfenidone or pyridone analog compound with non-encapsulating soluble excipients/salts), a complex liquid such as an aqueous liquid (*e.g.*, pirfenidone or pyridone analog compound encapsulated or complexed with soluble excipients such as lipids, liposomes, cyclodextrins, microencapsulations, and emulsions), a complex suspension (*e.g.*, pirfenidone or pyridone analog compound as a low-solubility, stable nanosuspension alone, as co-crystal/co-precipitate complexes, and/or as mixtures with low solubility lipids such as solid-lipid nanoparticles), a dry powder (*e.g.*, dry powder pirfenidone or pyridone analog compound alone or in co-crystal/co-precipitate/spray-dried complex or mixture with low solubility excipients/salts or readily soluble blends such as lactose), or an organic soluble or organic suspension solution, for packaging and administration using an inhalation device such as a metered-dose inhalation device.

Selection of a particular pirfenidone or pyridone analog compound formulation or pirfenidone or pyridone analog compound formulation composition as provided herein according to certain preferred embodiments may be influenced by the desired product packaging. Factors to be considered in selecting packaging may include, for example, intrinsic product stability, whether the formulation may be subject to lyophilization, device selection (*e.g.*, liquid nebulizer, dry-powder inhaler, meter-dose inhaler), and/or packaging form (*e.g.*, simple liquid or complex liquid formulation, whether provided in a vial as a liquid or as a lyophilisate to be dissolved prior to or upon insertion into the device; complex suspension formulation whether provided in a vial as a liquid or as a lyophilisate, and with or without a soluble salt/excipient component to be dissolved prior to or upon insertion into the

02 May 2016
2012212269

device, or separate packaging of liquid and solid components; dry powder formulations in a vial, capsule or blister pack; and other formulations packaged as readily soluble or low-solubility solid agents in separate containers alone or together with readily soluble or low-solubility solid agents.

5 Packaged agents may be manufactured in such a way as to be provide a pirfenidone or pyridone analog compound formulation composition for pulmonary delivery that comprises a solution which is provided as a pirfenidone or pyridone analog compound aqueous solution having a pH from about 3.0 to about 11.0, more preferably from about pH 4 to about pH 8, at a concentration of at least 0.1 mg/mL to about 50 mg/mL, and having a total osmolality at
10 least 50 mOsmol/kg to about 1000 mOsmol/kg, more preferably 200 to about 500 mOsmol/kg.

In some embodiments, the present invention relates to the aerosol and/or topical delivery of a pyridone analog compound (*e.g.*, pirfenidone). Pirfenidone has favorable solubility characteristics enabling dosing of clinically-desirable levels by aerosol (*e.g.*,
15 through liquid nebulization, dry powder dispersion or meter-dose administration) or topically (*e.g.*, aqueous suspension, oily preparation or the like or as a drip, spray, suppository, salve, or an ointment or the like), and can be used in methods for acute or prophylactic treatment of a subject having pulmonary fibrosis, or of a subject at risk for having pulmonary fibrosis. Clinical criteria for determining when pulmonary fibrosis is present, or when a subject is at
20 risk for having pulmonary fibrosis, are known to the art. Pulmonary delivery via inhalation permits direct and titrated dosing directly to the clinically-desired site with reduced systemic exposure.

In a preferred embodiment, the method treats or serves as prophylaxis against interstitial lung disease (ILD) by administering a pirfenidone or pyridone analog compound
25 formulation as an aerosol (*e.g.*, a suspension of liquid particles in air or another gas) to a subject having or suspected to have interstitial lung disease. Interstitial lung disease includes those conditions of idiopathic interstitial pneumonias as defined by American Thoracic Society/European Respiratory Society international multidisciplinary consensus classification of the idiopathic interstitial pneumonias, AM. J. Respir. Crit. Care Med. 165, 277-304 (2002).
30 These include ILD of known cause or association with connective tissue diseases, occupational causes or drug side effect, idiopathic interstitial pneumonias (*e.g.* idiopathic

02 May 2016
2012212269

pulmonary fibrosis, non-specific interstitial pneumonia, desquamative interstitial pneumonia, respiratory bronchiolitis-ILD, cryptogenic organizing pneumonia, acute interstitial pneumonia and lymphocytic interstitial pneumonia), granulomatous lung disease (e.g., sarcoidosis, hypersensitivity pneumonitis and infection), and other forms of ILD (e.g., lymphangioleiomyomatosis, pulmonary Langerhans' cell histiocytosis, eosinophilic pneumonia and pulmonary alveolar proteinosis).

The therapeutic method may also include a diagnostic step, such as identifying a subject with or suspected of having ILD. In some embodiments, the method further subclassifies into idiopathic pulmonary fibrosis. In some embodiments, the delivered amount of aerosol pirfenidone or pyridone analog compound (or salt thereof) formulation is sufficient to provide acute, sub-acute, or chronic symptomatic relief, slowing of fibrosis progression, halting fibrosis progression, reversing fibrotic damage, and/or subsequent increase in survival and/or improved quality of life.

The therapeutic method may also include a diagnostic step, such as identifying a subject with or suspected of having fibrosis in other tissues, by non-limiting example in the heart, liver, kidney or skin. In some embodiments, the delivered amount of liquid nebulized, dry powder or metered-dose aerosol pirfenidone or pyridone analog compound (or salt thereof) formulation is sufficient to provide acute, sub-acute, or chronic symptomatic relief, slowing of fibrosis progression, halting fibrosis progression, reversing fibrotic damage, and/or subsequent increase in survival and/or improved quality of life.

The therapeutic method may also include a diagnostic step, such as identifying a subject with or suspected of having multiple sclerosis. In some embodiments, the delivered amount of liquid nebulized, dry powder or metered-dose aerosol pirfenidone or pyridone analog compound (or salt thereof) formulation is sufficient to provide acute, sub-acute, or chronic symptomatic relief, slowing of demyelination progression, halting demyelination progression, reversing demyelinated damage, and/or subsequent increase in survival and/or improved quality of life.

In another embodiment, liquid nebulized, dry powder or metered-dose aerosol pirfenidone or pyridone analog compound (or salt thereof) may be co-administered, administered sequentially or prepared in a fixed-combination with antimicrobial agents to also provide therapy for a co-existing bacterial infection. By non-limiting example the

02 May 2016
2012212269

bacteria may be a gram-negative bacteria such as *Pseudomonas aeruginosa*, *Pseudomonas fluorescens*, *Pseudomonas acidovorans*, *Pseudomonas alcaligenes*, *Pseudomonas putida*, *Stenotrophomonas maltophilia*, *Burkholderia cepacia*, *Aeromonas hydrophilia*, *Escherichia coli*, *Citrobacter freundii*, *Salmonella typhimurium*, *Salmonella typhi*, *Salmonella paratyphi*,
5 *Salmonella enteritidis*, *Shigella dysenteriae*, *Shigella flexneri*, *Shigella sonnei*, *Enterobacter cloacae*, *Enterobacter aerogenes*, *Klebsiella pneumoniae*, *Klebsiella oxytoca*, *Serratia marcescens*, *Francisella tularensis*, *Morganella morganii*, *Proteus mirabilis*, *Proteus vulgaris*, *Providencia alcalifaciens*, *Providencia rettgeri*, *Providencia stuartii*, *Acinetobacter calcoaceticus*, *Acinetobacter haemolyticus*, *Yersinia enterocolitica*, *Yersinia pestis*, *Yersinia*
10 *pseudotuberculosis*, *Yersinia intermedia*, *Bordetella pertussis*, *Bordetella parapertussis*, *Bordetella bronchiseptica*, *Haemophilus influenzae*, *Haemophilus parainfluenzae*, *Haemophilus haemolyticus*, *Haemophilus parahaemolyticus*, *Haemophilus ducreyi*, *Pasteurella multocida*, *Pasteurella haemolytica*, *Branhamella catarrhalis*, *Helicobacter pylori*, *Campylobacter fetus*, *Campylobacter jejuni*, *Campylobacter coli*, *Borrelia*
15 *burgdorferi*, *Vibrio cholerae*, *Vibrio parahaemolyticus*, *Legionella pneumophila*, *Listeria monocytogenes*, *Neisseria gonorrhoeae*, *Neisseria meningitidis*, *Kingella*, *Moraxella*, *Gardnerella vaginalis*, *Bacteroides fragilis*, *Bacteroides distasonis*, *Bacteroides* 3452A
homology group, *Bacteroides vulgatus*, *Bacteroides ovalus*, *Bacteroides thetaiotaomicron*,
Bacteroides uniformis, *Bacteroides eggerthii*, and *Bacteroides splanchnicus*. In some
20 embodiments of the methods described above, the bacteria are gram-negative anaerobic
bacteria, by non-limiting example these include *Bacteroides fragilis*, *Bacteroides distasonis*,
Bacteroides 3452A homology group, *Bacteroides vulgatus*, *Bacteroides ovalus*, *Bacteroides*
thetaiotaomicron, *Bacteroides uniformis*, *Bacteroides eggerthii*, and *Bacteroides*
splanchnicus. In some embodiments of the methods described above, the bacteria are gram-
25 positive bacteria, by non-limiting example these include: *Corynebacterium diphtheriae*,
Corynebacterium ulcerans, *Streptococcus pneumoniae*, *Streptococcus agalactiae*,
Streptococcus pyogenes, *Streptococcus milleri* ; *Streptococcus* (Group G); *Streptococcus*
(Group C/F); *Enterococcus faecalis*, *Enterococcus faecium*, *Staphylococcus aureus*,
Staphylococcus epidermidis, *Staphylococcus saprophyticus*, *Staphylococcus intermedius*,
30 *Staphylococcus hyicus* subsp. *hyicus*, *Staphylococcus haemolyticus*, *Staphylococcus hominis*,
and *Staphylococcus saccharolyticus*. In some embodiments of the methods described above,

02 May 2016
2012212269

the bacteria are gram-positive anaerobic bacteria, by non-limiting example these include *Clostridium difficile*, *Clostridium perfringens*, *Clostridium tetini*, and *Clostridium botulinum*. In some embodiments of the methods described above, the bacteria are acid-fast bacteria, by non-limiting example these include *Mycobacterium tuberculosis*, *Mycobacterium avium*,
5 *Mycobacterium intracellulare*, and *Mycobacterium leprae*. In some embodiments of the methods described above, the bacteria are atypical bacteria, by non-limiting example these include *Chlamydia pneumoniae* and *Mycoplasma pneumoniae*.

As a non-limiting example, in a preferred embodiment, a pyridone analog compound as provided herein (e.g., pirfenidone) formulated to permit mist, gas-liquid suspension or
10 liquid nebulized, dry powder and/or metered-dose inhaled aerosol administration to supply effective concentrations or amounts to produce and maintain threshold drug concentrations in the lung and/or targeted downstream tissue, which may be measured as drug levels in epithelial lining fluid (ELF), sputum, lung tissue, bronchial lavage fluid (BAL), or by deconvolution of blood concentrations through pharmacokinetic analysis. One embodiment
15 includes the use of aerosol administration, delivering high or titrated concentration drug exposure directly to the affected tissue for treatment of pulmonary fibrosis and inflammation associated with ILD (including idiopathic pulmonary fibrosis), COPD and asthma in animals and humans. In one such embodiment, the peak lung ELF levels achieved following aerosol administration to the lung will be between 0.1 mg/mL and about 50 mg/mL pirfenidone or
20 pyridone analog. In another embodiment, the peak lung wet tissue levels achieved following aerosol administration to the lung will be between 0.004 mcg/gram lung tissue and about 500 mcg/gram lung tissue pirfenidone or pyridone analog.

As a non-limiting example, in a preferred embodiment, a pyridone analog compound as provided herein (e.g., pirfenidone) formulated to permit mist, gas-liquid suspension or
25 liquid nebulized, dry powder and/or metered-dose inhaled aerosol administration to supply effective concentrations or amounts to produce and maintain threshold drug concentrations in the blood and/or lung, which may be measured as drug levels in epithelial lining fluid (ELF), sputum, lung tissue, bronchial lavage fluid (BAL), or by deconvolution of blood concentrations through pharmacokinetic analysis that absorb to the pulmonary vasculature
30 producing drug levels sufficient for extra-pulmonary therapeutics, maintenance or prophylaxis. One embodiment includes the use of aerosol administration, delivering high

02 May 2016
2012212269

concentration drug exposure in the pulmonary vasculature and subsequent tissues and associated vasculature for treatment, maintenance and/or prophylaxis of, but not limited to cardiac fibrosis, kidney fibrosis, hepatic fibrosis, heart or kidney toxicity, or multiple sclerosis. In one such embodiment, the peak tissue-specific plasma levels (e.g., heart, kidney and liver) or cerebral spinal fluid levels (e.g. central nervous system) achieved following aerosol administration to the lung following oral inhalation or to the lung or nasal cavity following intra-nasal administration will be between 0.1 mcg/mL and about 50 mcg/mL pirfenidone or pyridone analog. In another embodiment, the peak lung wet tissue levels achieved following aerosol administration to the lung will be between 0.004 mcg/gram lung tissue and about 500 mcg/gram lung tissue pirfenidone or pyridone analog.

In another embodiment, a method is provided for acute or prophylactic treatment of a patient through non-oral or non-nasal topical administration of pirfenidone or pyridone analog (or a salt thereof) compound formulation to produce and maintain threshold drug concentrations at a burn site. One embodiment includes the use of aerosol administration, delivering high concentration drug exposure directly to the affected tissue for treatment or prevention of scarring in skin. For example according to these and related embodiments, the term aerosol may include a spray, mist, or other nucleated liquid or dry powder form.

In another embodiment, a method is provided for acute or prophylactic treatment of a patient through non-oral or non-nasal topical administration of pirfenidone or pyridone analog (or a salt thereof) compound formulation to produce and maintain threshold drug concentrations in the eye. One embodiment includes the use of aerosol administration or formulation drops to deliver high concentration drug exposure directly to the affected tissue for treatment or prevention of scarring following surgical glaucoma surgery (e.g., bleb fibrosis). For example according to these and related embodiments, the term aerosol may include a spray, mist, or other nucleated liquid or dry powder form. A drop may be simple liquid or suspension formulation.

In another embodiment, a pyridone analog compound as provided herein (e.g., pirfenidone) formulation by inhalation, wherein the inhaled liquid aerosol (e.g., following liquid nebulization or metered-dose administration) or dry powder aerosol has a mean particle size from about 1 micron to 10 microns mass median aerodynamic diameter and a particle size geometric standard deviation of less than or equal to about 3 microns. In another

02 May 2016
2012212269

embodiment, the particle size is 2 microns to about 5 microns mass median aerodynamic diameter and a particle size geometric standard deviation of less than or equal to about 3 microns. In one embodiment, the particle size geometric standard deviation is less than or equal to about 2 microns.

5 As a non-limiting example, in a preferred embodiment, a pyridone analog compound as provided herein (*e.g.*, pirfenidone) remains at the therapeutically effective concentration at the site of pulmonary pathology, suspected pulmonary pathology, and/or site of pulmonary absorption into the pulmonary vasculature for at least about 1 minute, at least about a 5 minute period, at least about a 10 min period, at least about a 20 min period, at least about a 30 min period, at least about a 1 hour period, at least a 2 hour period, at least about a 4 hour period, at least an 8 hour period, at least a 12 hour period, at least a 24 hour period, at least a 48 hour period, at least a 72 hour period, or at least one week. The effective pirfenidone or pyridone analog concentration is sufficient to cause a therapeutic effect and the effect may be localized or broad-acting to or from the site of pulmonary pathology.

15 As a non-limiting example, in a preferred embodiment, a pyridone analog compound as provided herein (*e.g.*, pirfenidone or salt thereof) following inhalation administration remains at the therapeutically effective concentration at the site of cardiac fibrosis, kidney fibrosis, hepatic fibrosis, heart or kidney toxicity, or multiple sclerosis demyelination for at least about 1 minute, at least about a 5 minute period, at least about a 10 min period, at least about a 20 min period, at least about a 30 min period, at least about a 1 hour period, at least a 2 hour period, at least about a 4 hour period, at least an 8 hour period, at least a 12 hour period, at least a 24 hour period, at least a 48 hour period, at least a 72 hour period, or at least one week. The effective pirfenidone or pyridone analog concentration is sufficient to cause a therapeutic effect and the effect may be localized or broad-acting to or from the site of

25 extrapulmonary pathology.

In some embodiments, delivery sites such as a pulmonary site, the a pirfenidone or pyridone analog compound formulation as provided herein is administered in one or more administrations so as to achieve a respirable delivered dose daily of pirfenidone or pyridone analog of at least about 0.1 mg to about 50 mg, including all integral values therein such as

30 0.1, 0.2, 0.4, 0.8, 1, 2, 4, 6, 10, 15, 20, 25, 30, 35, 40, 45, 50 milligrams. In some embodiments, a pirfenidone or pyridone analog compound formulation as provided herein is

02 May 2016
2012212269

administered in one or more administrations so as to achieve a respirable delivered dose daily of pirfenidone or pyridone analog of at least about 0.1 mg to about 300 mg, including all integral values therein such as 0.1, 0.2, 0.4, 0.8, 1, 2, 4, 6, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 95, 100, 105, 110, 115, 120, 125, 130, 135, 140, 145, 150, 155, 160, 165, 170, 175, 180, 185, 190, 195, 200, 205, 210, 215, 220, 225, 230, 235, 240, 245, 250, 255, 260, 265, 270, 275, 280, 285, 290, 295, 300 milligrams. The pirfenidone or pyridone analog formulation is administered in the described respirable delivered dose in less than 60 minutes, less than 50 minutes, less than 40 minutes, less than 30 minutes, less than 20 minutes, less than 15 minutes, less than 10 minutes, less than 7 minutes, less than 5 minutes, in less than 3 minutes, in less than 2 minutes, in less than 1 minute, 10 inhalation breaths, 8 inhalation breaths, 6 inhalation breaths, 4 inhalation breaths, 3 inhalation breaths, 2 inhalation breaths or 1 inhalation breath. In some embodiments, pirfenidone or pyridone analog formulation is administered in the described respirable delivered dose using a breathing pattern of 1 second inhalation and 2 seconds exhalation, 2 seconds inhalation and 2 seconds exhalation, 3 seconds inhalation and 2 seconds exhalation, 4 seconds inhalation and 2 seconds exhalation, 5 seconds inhalation and 2 seconds exhalation, 6 seconds inhalation and 2 seconds exhalation, 7 seconds inhalation and 2 seconds exhalation, and 8 seconds inhalation and 2 seconds exhalation.

In some embodiments, delivery sites such as the nasal cavity or sinus, pirfenidone or pyridone analog (or salt thereof) compound formulation is administered in one or more administrations so as to achieve a nasal cavity or sinus deposited dose daily of pirfenidone or pyridone analog of at least about 0.1 mg to about 50 mg, including all integral values therein such as 0.1, 0.2, 0.4, 0.8, 1, 2, 4, 6, 10, 15, 20, 25, 30, 35, 40, 45, 50 milligrams. In some embodiments, delivery sites such as the nasal cavity or sinus, pirfenidone or pyridone analog (or salt thereof) compound formulation is administered in one or more administrations so as to achieve a nasal cavity or sinus deposited dose daily of pirfenidone or pyridone analog of at least about 0.1 mg to about 300 mg, including all integral values therein such as 0.1, 0.2, 0.4, 0.8, 1, 2, 4, 6, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 95, 100, 105, 110, 115, 120, 125, 130, 135, 140, 145, 150, 155, 160, 165, 170, 175, 180, 185, 190, 195, 200, 205, 210, 215, 220, 225, 230, 235, 240, 245, 250, 255, 260, 265, 270, 275, 280, 285, 290, 295, 300 milligrams. The pirfenidone or pyridone analog formulation is

02 May 2016
2012212269

administered in the described nasal or sinus deposited dose in less than 20 minutes, less than 15 minutes, less than 10 minutes, less than 7 minutes, less than 5 minutes, in less than 3 minutes, in less than 2 minutes, in less than 1 minute, 10 intranasal inhalation breaths, 8 intranasal inhalation breaths, 6 intranasal inhalation breaths, 4 intranasal inhalation breaths, 3 intranasal inhalation breaths, 2 intranasal inhalation breaths or 1 intranasal inhalation breath. In some embodiments, pirfenidone or pyridone analog formulation is administered in the described respirable delivered dose using a breathing pattern of 1 second inhalation and 2 seconds exhalation, 2 seconds inhalation and 2 seconds exhalation, 3 seconds inhalation and 2 seconds exhalation, 4 seconds inhalation and 2 seconds exhalation, 5 seconds inhalation and 2 seconds exhalation, 6 seconds inhalation and 2 seconds exhalation, 7 seconds inhalation and 2 seconds exhalation, and 8 seconds inhalation and 2 seconds exhalation.

In some embodiments of the methods described above, the subject is a human. In some embodiments of the methods described above, the subject is a human with ILD. In some embodiments, the method further sub-classifies into idiopathic pulmonary fibrosis. In some embodiments of the methods describe above, the human subject may be mechanically ventilated.

In embodiments where a human is mechanically ventilated, aerosol administration would be performed using an in-line device (by non-limiting example, the Nektar Aeroneb Pro) or similar adaptor with device for liquid nebulization. Aerosol administration could also be performed using an in-line adaptor for dry powder or metered-dose aerosol generation and delivery.

In some embodiments of the methods described above, the subject is a human. In some embodiments of the methods described above, the subject is a human requiring cardiac fibrosis therapy. In some embodiments of the methods describe above, the human subject may be mechanically ventilated.

In some embodiments of the methods described above, the subject is a human. In some embodiments of the methods described above, the subject is a human requiring kidney fibrosis therapy. In some embodiments of the methods describe above, the human subject may be mechanically ventilated.

In some embodiments of the methods described above, the subject is a human. In some embodiments of the methods described above, the subject is a human requiring hepatic

02 May 2016
2012212269

fibrosis therapy. In some embodiments of the methods describe above, the human subject may be mechanically ventilated.

In some embodiments of the methods described above, the subject is a human. In some embodiments of the methods described above, the subject is a human requiring cardiac or kidney toxicity therapy. In some embodiments of the methods describe above, the human subject may be mechanically ventilated.

In some embodiments of the methods described above, the subject is a human. In some embodiments of the methods described above, the subject is a human requiring COPD therapy. In some embodiments of the methods describe above, the human subject may be mechanically ventilated.

In some embodiments of the methods described above, the subject is a human. In some embodiments of the methods described above, the subject is a human requiring asthma therapy. In some embodiments of the methods describe above, the human subject may be mechanically ventilated.

In some embodiments of the methods described above, the subject is a human. In some embodiments of the methods described above, the subject is a human requiring multiple sclerosis therapy. In some embodiments of the methods describe above, the human subject may be mechanically ventilated.

In another embodiment, a pharmaceutical composition is provided that includes a simple liquid pirfenidone or pyridone analog (or salt thereof) compound formulation with non-encapsulating water soluble excipients as described above having an osmolality from about 50 mOsmol/kg to about 6000 mOsmol/kg. In one embodiment, the osmolality is from about 50 mOsmol/kg to about 1000 mOsmol/kg. In one embodiment, the osmolality is from about 400 mOsmol/kg to about 5000 mOsmol/kg. In other embodiments the osmolality is from about 50, 100, 150, 200, 250, 300, 350, 400, 450, 500 mOsmol/kg to about 1000, 1100, 1200, 1300, 1400, 1500, 1600, 1700, 1800, 1900, 2000, 2200, 2400, 2600, 2800, 3000, 3200, 3400, 3600, 3800, 4000, 4200, 4400, 4600, 4800m 5000, 5200, 5400, 5600, 5800 and 6000 mOsmol/kg. With respect to osmolality, and also elsewhere in the present application, “about” when used to refer to a quantitative value means that a specified quantity may be greater than or less than the indicated amount by 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20 percent of the stated numerical value.

02 May 2016

2012212269

In another embodiment, a pharmaceutical composition is provided that includes a simple liquid pirfenidone or pyridone analog (or salt thereof) compound formulation having a permeant ion concentration between from about 30 mM to about 300 mM and preferably between from about 50mM to 200 mM. In one such embodiment, one or more permeant ions in the composition are selected from the group consisting of chloride and bromide.

In another embodiment, a pharmaceutical composition is provided that includes a complex liquid pirfenidone or pyridone analog (or salt thereof) compound formulation encapsulated or complexed with water soluble excipients such as lipids, liposomes, cyclodextrins, microencapsulations, and emulsions) as described above having a solution osmolality from about 50 mOsmol/kg to about 6000 mOsmol/kg. In one embodiment, the osmolality is from about 50 mOsmol/kg to about 1000 mOsmol/kg. In one embodiment, the osmolality is from about 100 mOsmol/kg to about 500 mOsmol/kg. In one embodiment, the osmolality is from about 400 mOsmol/kg to about 5000 mOsmol/kg.

In another embodiment, a pharmaceutical composition is provided that includes a complex liquid pirfenidone or pyridone analog (or salt thereof) compound formulation having a permeant ion concentration from about 30 mM to about 300 mM. In one such embodiment, one or more permeant ions in the composition are selected from the group consisting of chloride and bromide.

In another embodiment, a pharmaceutical composition is provided that includes a complex liquid pirfenidone or pyridone analog (or salt thereof) compound formulation having a permeant ion concentration from about 50 mM to about 200 mM. In one such embodiment, one or more permeant ions in the composition are selected from the group consisting of chloride and bromide.

In another embodiment, a pharmaceutical composition is provided that includes a simple liquid formulation of pirfenidone or pyridone analog (or salt thereof) compound formulation having a pirfenidone or pyridone analog to multivalent cation positive charge molar ratio between about two pirfenidone or pyridone analog compounds to about 0.1 to about 4 multivalent cation positive charges. By non-limiting example, two pirfenidone or pyridone analog compounds to one magnesium ion (two cation positive charges), three pirfenidone or pyridone analog compounds to one magnesium ions, four pirfenidone or

02 May 2016
2012212269

pyridone analog compounds to one magnesium ions, and two pirfenidone or pyridone analog compounds to two magnesium ions.

An unexpected finding was that divalent cations, by non-limiting example magnesium, reduced pirfenidone dissolution time and increased pirfenidone aqueous solubility in a molar ratio-dependent manner. This increased saturation solubility is enabling to deliver predicted-sufficient quantities of inhaled liquid-nebulized pirfenidone to the lung. By example, one pirfenidone molecules to three magnesium molecules exhibited a slower dissolution time and reduced saturation solubility than one pirfenidone molecule to one magnesium molecule. Moreover, one pirfenidone molecules to one magnesium molecule exhibited a faster dissolution time and greater aqueous solubility than an equal-molar ratio of pirfenidone to sodium.

In another embodiment, a pharmaceutical composition is provided that includes a complex liquid formulation of pirfenidone or pyridone analog (or salt thereof) compound formulation having a pirfenidone or pyridone analog to to about 0.1 to about 4 multivalent cation positive charges. By non-limiting example, two pirfenidone or pyridone analog compounds to one magnesium ion (two cation positive charges), three pirfenidone or pyridone analog compounds to one magnesium ions, four pirfenidone or pyridone analog compounds to one magnesium ions, and two pirfenidone or pyridone analog compounds to two magnesium ions.

In another embodiment, a pharmaceutical composition is provided that includes a complex liquid pirfenidone or pyridone analog (or salt thereof) compound formulation as a low water-soluble stable nanosuspension alone or in co-crystal/co-precipitate complexes, or mixtures with low solubility lipids, such as lipid nanosuspensions) as described above having a solution osmolality from about 50 mOsmol/kg to about 6000 mOsmol/kg. In one embodiment, the osmolality is from about 100 mOsmol/kg to about 500 mOsmol/kg. In one embodiment, the osmolality is from about 400 mOsmol/kg to about 5000 mOsmol/kg.

In another embodiment, a pharmaceutical composition is provided that includes a complex suspension of a pirfenidone or pyridone analog (or salt thereof) compound formulation having a permeant ion concentration from about 30 mM to about 300 mM. In one such embodiment, one or more permeant ions in the composition are selected from the group consisting of chloride and bromide.

02 May 2016

2012212269

In another embodiment, a pharmaceutical composition is provided that includes a complex suspension of a pirfenidone or pyridone analog (or salt thereof) compound formulation having a permeant ion concentration from about 50 mM to about 200 mM. In one such embodiment, one or more permeant ions in the composition are selected from the group consisting of chloride and bromide.

In another embodiment, a pharmaceutical composition is provided that includes a complex suspension of pirfenidone or pyridone analog (or salt thereof) compound formulation having a pirfenidone or pyridone analog to multivalent cation positive charge molar ratio between about one pirfenidone or pyridone analog compounds to about 0.1 to about 4 multivalent cation positive charges. By non-limiting example, two pirfenidone or pyridone analog compounds to one magnesium ion (two cation positive charges), three pirfenidone or pyridone analog compounds to one magnesium ions, four pirfenidone or pyridone analog compounds to one magnesium ions, and two pirfenidone or pyridone analog compounds to two magnesium ions.

In other embodiments, a pirfenidone or pyridone analog (or salt thereof) compound formulation as provided herein, or a pharmaceutical composition, is provided that includes a taste-masking agent. As non-limiting examples, a taste-masking agent may include a sugar, saccharin (*e.g.*, sodium saccharin), sweetener or other compound or agent that beneficially affects taste, after-taste, perceived unpleasant saltiness, sourness or bitterness, or that reduces the tendency of an oral or inhaled formulation to irritate a recipient (*e.g.*, by causing coughing or sore throat or other undesired side effect, such as may reduce the delivered dose or adversely influence patient compliance with a prescribed therapeutic regimen). Certain taste-masking agents may form complexes with a pirfenidone or pyridone analog (or salt thereof) compound.

In certain preferred embodiments that relate to the pirfenidone or pyridone analog (or salt thereof) compound formulations disclosed herein, the formulation comprises a pirfenidone or pyridone analog (or salt thereof) compound and a taste-masking agent and may be optimized with respect to a desired osmolality, and/or an optimized permeant ion concentration. In certain such embodiments, the taste-masking agent comprises saccharin (*e.g.*, sodium saccharin), which according to non-limiting theory affords certain advantages associated with the ability of this taste-masking agent to provide desirable taste effects even

02 May 2016
2012212269

when present in extremely low concentrations, such as may have little or no effect on the detectable osmolality of a solution, thereby permitting the herein described formulations to deliver aqueous solutions, organic or dry powder formulations in a well-tolerated manner. In certain such embodiments, the taste-masking agent comprises a chelating agent (*e.g.*, EDTA or divalent cation such as magnesium), which according to non-limiting theory affords certain advantages associated with the ability of this taste-masking agent to provide desirable taste effects by masking taste-stimulating chemical moieties on pirfenidone or pyridone analog. With divalent cations, inclusion as a taste-masking agent may also substitute as an osmolality adjusting agent, and pending the salt form may also provide the permeant ion (*e.g.*, magnesium chloride), thereby permitting the herein described formulations to deliver aqueous solutions, organic or dry powder formulations in a well-tolerated manner. Non-limiting examples of these and related embodiments include a pirfenidone or pyridone analog (or salt thereof) compound formulation for pulmonary delivery as described herein that comprises an aqueous solution having a pH of from about 4 to about 8 and an osmolality of from about 50 to about 1000 mOsmol/kg (*e.g.*, adjusted with sodium chloride), the solution comprising pirfenidone or pyridone analog (or salt thereof) compound and sodium saccharin where the aqueous solution contains from about 0.1 mM to about 2.0 mM saccharin. A related non-limiting example further comprises citrate (*e.g.*, citric acid) in an aqueous solution containing from about 1 mM to about 100 mM citrate. A related non-limiting example further comprises or replace citrate with phosphate (*e.g.*, sodium phosphate) in an aqueous solution containing from about 0.0 mM to about 100 mM phosphate. Another related non-limiting example further comprises or replace citrate with phosphate (*e.g.*, sodium phosphate) in an aqueous solution containing from about 0.5 mM to about 100 mM phosphate. By another non-limiting examples, these and related embodiments include a pirfenidone or pyridone analog (or salt thereof) compound formulation for pulmonary delivery as described herein that comprises an aqueous solution having a pH of from about 4 to about 8 and an osmolality of from about 50 to about 5000 mOsmol/kg (*e.g.*, adjusted with magnesium chloride), the solution comprising pirfenidone or pyridone analog (or salt thereof) compound, wherein a divalent cation (*e.g.*, berilium, magnesium, or calcium) serves both to adjust osmolality and as a taste-masking agent. Where included as a taste-masking agent, divalent cation (*e.g.*, magnesium) is added stoichiometrically with pirfenidone or pyridone

02 May 2016
2012212269

analog. By example, 1 mol divalent ion to 2 mols pirfenidone or pyridone analog, 1.5 mols divalent ion to 2 mols pirfenidone or pyridone analog, 2 mols divalent ion to 2 mols pirfenidone or pyridone analog, 3 mols divalent ion to 2 mols pirfenidone or pyridone analog, or 4 mols divalent ion to 2 mols pirfenidone or pyridone analog. Where osmolality required further increase sodium chloride or additional divalent salt may be used. A related non-limiting example further comprises citrate (*e.g.*, citric acid) in an aqueous solution containing from about 1 mM to about 100 mM citrate. A related non-limiting example citrate is replaced with phosphate (*e.g.*, sodium phosphate) in an aqueous solution containing from about 0.0 mM to about 100 mM phosphate. In another related non-limiting example citrate is replaced with phosphate (*e.g.*, sodium phosphate) in an aqueous solution containing from about 0.0 mM to about 100 mM phosphate.

In another embodiment, while the inclusion of the correct molar ratio of magnesium to pirfenidone reduces dissolution time and increases saturation solubility to a level required for sufficient liquid nebulization delivery to the lung, an unexpected finding was that this formulation additionally requires a taste masking agent for acute tolerability upon inhalation of a nebulized solution. To this end, between 0.1 and 1.0 micromolar saccharin enables the use of this solubility-enabling formulation.

In another embodiment, a pharmaceutical composition may be protected from light to avoid photodegradation. By non-limiting example, this may occur by light-protected vials, ampoules, blisters, capsules, or other colored or light-protected primary packaging. By another non-limiting example, this may occur by use of secondary packaging such as an aluminum or other light-protected over-pouch, box or other secondary packaging.

In another embodiment, a pharmaceutical composition may be protected from oxygen to protect from oxidation. By non-limiting example, in solution this may occur by removing oxygen from solution prior to or during compounding (*e.g.*, sparging), and or controlled the primary packaging head-space gas (*e.g.* using of inert gas such as argon or nitrogen in the head space). Similarly, by another non-limiting example, controlling the included secondary packaging gas (*e.g.* with inert gas) may also be required. For powder formulations this may be controlled by use of insert gas in primary and/or secondary packaging. Meter-dose inhaled products may benefit by the same means as described above for solution products.

02 May 2016
2012212269

In another embodiment, pirfenidone or pyridone analog present in a pharmaceutical composition may be protected from hydrolysis by inclusion of a cationic metal ion. By non-limiting example, acid hydrolysis of amide bonds decreases with an increased salt concentration. Specifically, hydration number is important for this rate decrease, as electrolyte hydration decreases the availability of free water for the reaction. Thus, the rate decreases with increased salt and increased hydration number. The order of increasing hydration number: potassium < sodium < lithium < magnesium. The rate decrease also nearly parallels ionic strength. By non-limiting example, the addition of magnesium will stabilize the 2-pyridone structure of pirfenidone. It is known that pirfenidone chelates Fe(III) at a ratio of 3 pirfenidone molecules to 1 Fe(III). From this it follows that pirfenidone will chelate magnesium at 2 pirfenidone molecules to 1 magnesium +2 charge. Therefore, for this purpose the addition of magnesium or other cationic metal ion may be stoichiometric to the amount of pirfenidone or pyridone analog. By non-limiting example, 2 pirfenidone molecules to 0.1 magnesium molecules, 2 pirfenidone molecules to 0.25 magnesium molecules, 2 pirfenidone molecules to 0.5 magnesium molecules, 2 pirfenidone molecules to 0.75 magnesium molecules, 2 pirfenidone molecules to 1 magnesium molecules, 2 pirfenidone molecules to 1.5 magnesium molecules, 2 pirfenidone molecules to 2 magnesium molecules, 2 pirfenidone molecules to 3 magnesium molecules, 2 pirfenidone molecules to 4 magnesium molecules, 2 pirfenidone molecules to 5 magnesium molecules, 2 pirfenidone molecules to 6 magnesium molecules, 2 pirfenidone molecules to 7 magnesium molecules, 2 pirfenidone molecules to 8 magnesium molecules, 2 pirfenidone molecules to 9 magnesium molecules, 2 pirfenidone molecules to 10 magnesium molecules, 2 pirfenidone molecules to 12 magnesium molecules, 2 pirfenidone molecules to 14 magnesium molecules, 2 pirfenidone molecules to 16 magnesium molecules, 2 pirfenidone molecules to 18 magnesium molecules, or 2 pirfenidone molecules to 20 magnesium molecules. Potassium, sodium, lithium or iron may substitute for magnesium in these ratios and pharmaceutical composition. Included in the above pharmaceutical composition is the maintenance of the buffers described herein, at a pH from about 4.0 to about 8.0, and include MgCl₂ or cationic salt thereof at a level that provides an osmolality of 300 mOsmo/kg and 600 mOsmo/kg. While 300 mOsmo/kg is discussed in the literature as important for acute tolerability upon inhalation of this in a nebulized solution, 600 mOsmo/kg has been shown in unpublished

02 May 2016
2012212269

studies to be well tolerated with other drug solutions. However, a final solution osmolality up to 6000 mOsm/kg is contemplated. Unexpectedly, formulations described herein demonstrate good tolerability at high osmolalities.

In another embodiment, a pharmaceutical composition of liquid pirfenidone or pyridone analog may contain a solubility enhancing agent or co-solvent. By non-limiting example, these may include ethanol, cetylpyridinium chloride, glycerin, lecithin, propylene glycol, polysorbate (including polysorbate 20, 40, 60, 80 and 85), sorbitan triolate, and the like. By further example, cetylpyridinium chloride may be used from about 0.01 mg/mL to about 4 mg/mL pharmaceutical composition. Similarly, by another non-limiting example, ethanol may be used from about 0.01% to about 30% pharmaceutical composition. Similarly, by another non-limiting example, glycerin may be used from about 0.01% to about 25% pharmaceutical composition. Similarly, by another non-limiting example, lecithin may be used from about 0.01% to about 4% pharmaceutical composition. Similarly, by another non-limiting example, propylene glycol may be used from about 0.01% to about 30% pharmaceutical composition. Similarly, by another non-limiting example, polysorbates may also be used from about 0.01% to about 10% pharmaceutical composition. Similarly, by another non-limiting example, sorbitan triolate may be used from about 0.01% to about 20% pharmaceutical composition.

In another embodiment, a pharmaceutical composition of liquid or dry powder pirfenidone or pyridone analog may contain a chelated metal ion to assist in solubility and/or dissolution of pirfenidone or pyridone analog. By non-limiting example, these may include iron, magnesium, or calcium.

In another embodiment, a pharmaceutical composition of liquid or dry powder pirfenidone or pyridone analog may contain a chelated metal ion to assist in scavenging reactive oxygen species. By non-limiting example, these may include iron, magnesium, or calcium. By non-limiting example, for this purpose the addition of magnesium or other cationic metal ion may be stoichiometric to the amount of pirfenidone or pyridone analog. By non-limiting example, 2 pirfenidone molecules to 0.1 magnesium molecules, 2 pirfenidone molecules to 0.25 magnesium molecules, 2 pirfenidone molecules to 0.5 magnesium molecules, 2 pirfenidone molecules to 0.75 magnesium molecules, 2 pirfenidone molecules to 1 magnesium molecules, 2 pirfenidone molecules to 1.5 magnesium molecules,

02 May 2016
2012212269

2 pirfenidone molecules to 2 magnesium molecules, 2 pirfenidone molecules to 3 magnesium molecules, 2 pirfenidone molecules to 4 magnesium molecules, 2 pirfenidone molecules to 5 magnesium molecules, 2 pirfenidone molecules to 6 magnesium molecules, 2 pirfenidone molecules to 7 magnesium molecules, 2 pirfenidone molecules to 8 magnesium molecules, 2 pirfenidone molecules to 9 magnesium molecules, 2 pirfenidone molecules to 10 magnesium molecules, 2 pirfenidone molecules to 12 magnesium molecules, 2 pirfenidone molecules to 14 magnesium molecules, 2 pirfenidone molecules to 16 magnesium molecules, 2 pirfenidone molecules to 18 magnesium molecules, or 2 pirfenidone molecules to 20 magnesium molecules. Potassium, sodium, lithium or iron may substitute for magnesium in these ratios and pharmaceutical composition. Included in the above pharmaceutical composition is the maintenance of the buffers described herein, at a pH from about 4.0 to about 8.0, and include $MgCl_2$ or cationic salt thereof at a level that provides an osmolality of 300 mOsmo/kg and 600 mOsmo/kg. While 300 mOsmo/kg is discussed in the literature as important for acute tolerability upon inhalation of this in a nebulized solution, 600 mOsmo/kg has been shown in unpublished studies to be well tolerated with other drug solutions. However, a final solution osmolality up to 5000 mOsmo/kg is contemplated.

In some embodiments, described herein is a pharmaceutical composition that includes: pirfenidone; water; phosphate buffer or citrate buffer; and optionally sodium chloride or magnesium chloride. In other embodiments, described herein is a pharmaceutical composition that includes: pirfenidone; water; a buffer; and at least one additional ingredient selected from sodium chloride, magnesium chloride, ethanol, propylene glycol, glycerol, polysorbate 80, and cetylpyridinium bromide (or chloride). In some embodiments, the buffer is phosphate buffer. In other embodiments, the buffer is citrate buffer. In some embodiments, the pharmaceutical composition includes 1 mg to 500 mg of pirfenidone, for example, 5 mg, 10 mg, 15 mg, 25 mg, 37.5 mg, 75 mg, 100 mg, 115 mg, 150 mg, 190 mg, 220 mg, or 500 mg. In some embodiments, the osmolality of the pharmaceutical composition described herein is between about 50 mOsmo/kg to 6000 mOsmo/kg. In some embodiments, the pharmaceutical composition optionally includes saccharin (e.g. sodium salt). Non-limiting examples of pharmaceutical compositions described herein include any one of the pharmaceutical compositions described in Tables 1-1 to Table 1-11 of Example 1.

02 May 2016
2012212269

Solutions of pirfenidone should remain protected from light as the API in solution is subject to degradation

In another embodiment, a pharmaceutical composition is provided that includes a simple dry powder pirfenidone or pyridone analog (or salt thereof) compound alone in dry powder form with or without a blending agent such as lactose.

In another embodiment, the pharmaceutical composition used in a liquid, dry powder or meter-dose inhalation device is provided such that pirfenidone or pyridone analog is not in a salt form.

In another embodiment, a pharmaceutical composition is provided that includes a complex dry powder pirfenidone or pyridone analog (or salt thereof) compound formulation in co-crystal/co-precipitate/spray dried complex or mixture with low water soluble excipients/salts in dry powder form with or without a blending agent such as lactose.

In another embodiment, a system is provided for administering a pirfenidone or pyridone analog (or salt thereof) compound that includes a container comprising a solution of a pirfenidone or pyridone analog (or salt thereof) compound formulation and a nebulizer physically coupled or co-packaged with the container and adapted to produce an aerosol of the solution having a particle size from about 1 microns to about 5 microns mean mass aerodynamic diameter, volumetric mean diameter (VMD) or mass median diameter (MMD) and a particle size geometric standard deviation of less than or equal to about 2.5 microns mean mass aerodynamic diameter. In one embodiment, the particle size geometric standard deviation is less than or equal to about 3.0 microns. In one embodiment, the particle size geometric standard deviation is less than or equal to about 2.0 microns.

In another embodiment, a system is provided for administering a pirfenidone or pyridone analog (or salt thereof) compound that includes a container comprising a dry powder of a pirfenidone or pyridone analog (or salt thereof) compound and a dry powder inhaler coupled to the container and adapted to produce a dispersed dry powder aerosol having a particle size from about 1 microns to about 5 microns mean mass aerodynamic and a particle size standard deviation of less than or equal to about 3.0 microns. In one embodiment, the particle size standard deviation is less than or equal to about 2.5 microns. In one embodiment, the particle size standard deviation is less than or equal to about 2.0 microns.

02 May 2016
2012212269

In another embodiment, a kit is provided that includes a container comprising a pharmaceutical formulation comprising a pirfenidone or pyridone analog (or salt thereof) compound and an aerosolizer adapted to aerosolize the pharmaceutical formulation (*e.g.*, in certain preferred embodiments, a liquid nebulizer) and deliver it to the lower respiratory tract, for instance, to a pulmonary compartment such as alveoli, alveolar ducts and/or bronchioles, following intraoral administration. The formulation may also be delivered as a dry powder or through a metered-dose inhaler.

In another embodiment, a kit is provided that includes a container comprising a pharmaceutical formulation comprising a pirfenidone or pyridone analog (or salt thereof) compound and an aerosolizer adapted to aerosolize the pharmaceutical formulation (*e.g.*, in certain preferred embodiments, a liquid nebulizer) and deliver it to a nasal cavity following intranasal administration. The formulation may also be delivered as a dry powder or through a metered-dose inhaler.

It should be understood that many carriers and excipients may serve several functions, even within the same formulation.

Contemplated pharmaceutical compositions provide a therapeutically effective amount of pirfenidone or pyridone analog compound enabling, for example, once-a-day, twice-a-day, three times a day, etc. administration. In some embodiments, pharmaceutical compositions for inhaled delivery provide an effective amount of pirfenidone or pyridone analog compound enabling once-a-day dosing. In some embodiments, pharmaceutical compositions for inhaled delivery provide an effective amount of pirfenidone or pyridone analog compound enabling twice-a-day dosing. In some embodiments, pharmaceutical compositions for inhaled delivery provide an effective amount of pirfenidone or pyridone analog compound enabling three times-a-day dosing.

It is to be understood that both the foregoing general description and the following detailed description are exemplary and explanatory only and are not restrictive of the invention, as claimed.

Certain Terminology

The term “mg” refers to milligram.

The term “mcg” refers to microgram.

02 May 2016

2012212269

The term “microM” refers to micromolar.

The term “QD” refers to once a day dosing.

The term “BID” refers to twice a day dosing.

The term “TID” refers to three times a day dosing.

The term “QID” refers to four times a day dosing.

As used herein, the term “about” is used synonymously with the term “approximately.” Illustratively, the use of the term “about” with regard to a certain therapeutically effective pharmaceutical dose indicates that values slightly outside the cited values, .e.g., plus or minus 0.1% to 10%, which are also effective and safe.

As used herein, the terms “comprising,” “including,” “such as,” and “for example” are used in their open, non-limiting sense.

The terms “administration” or “administering” and “delivery” or “delivery” refer to a method of giving to a mammal a dosage of a therapeutic or prophylactic formulation, such as a pirfenidone or pyridone analog (or salt thereof) compound formulation described herein, for example as an anti-inflammatory, anti-fibrotic and/or anti-demyelination pharmaceutical composition, or for other purposes. The preferred delivery method or method of administration can vary depending on various factors, *e.g.*, the components of the pharmaceutical composition, the desired site at which the formulation is to be introduced, delivered or administered, the site where therapeutic benefit is sought, or the proximity of the initial delivery site to the downstream diseased organ (*e.g.*, aerosol delivery to the lung for absorption and secondary delivery to the heart, kidney, liver, central nervous system or other diseased destination). In some embodiments, pharmaceutical compositions described herein are administered by pulmonary administration.

The terms “pulmonary administration” or “inhalation” or “pulmonary delivery” or “oral inhalation” or “intranasal inhalation” and other related terms refer to a method of giving to a mammal a dosage of a therapeutic or prophylactic formulation, such as a pirfenidone or pyridone analog (or salt thereof) compound formulation described herein, by a route such that the desired therapeutic or prophylactic agent is delivered to the lungs of a mammal. Such delivery to the lung may occur by intranasal administration, oral inhalation administration.

Each of these routes of administration may occur as inhalation of an aerosol of formulations

02 May 2016
2012212269

described herein. In some embodiments, pulmonary administration occurs by passively delivering an aerosol described herein by mechanical ventilation.

The terms “intranasal inhalation administration” and “intranasal inhalation delivery” refer to a method of giving to a mammal a dosage of a pirfenidone or pyridone analog (or salt thereof) compound formulation described herein, by a route such that the formulation is targeting delivery and absorption of the therapeutic formulation directly in the lungs of the mammal through the nasal cavity. In some embodiments, intranasal inhalation administration is performed with a nebulizer.

The terms “intranasal administration” and “intranasal delivery” refer to a method of giving to a mammal a dosage of a therapeutic or prophylactic formulation, such as a pirfenidone or pyridone analog (or salt thereof) compound formulation described herein, by a route such that the desired therapeutic or prophylactic agent is delivered to the nasal cavity or diseased organs downstream (e.g., aerosol delivery to the nasal cavity for absorption and secondary delivery to the central nervous system or other diseased destination). Such delivery to the nasal cavity may occur by intranasal administration, wherein this route of administration may occur as inhalation of an aerosol of formulations described herein, injection of an aerosol of formulations described herein, gavage of a formulation described herein, or passively delivered by mechanical ventilation.

The terms “intraocular administration” and “intraocular delivery” refer to a method of giving to a mammal a dosage of a therapeutic or prophylactic formulation, such as a pirfenidone or pyridone analog (or salt thereof) compound formulation described herein, by a route such that the desired therapeutic or prophylactic agent is delivered to the eye. Such delivery to the eye may occur by direct administration to the eye. This route of administration may occur as spray of an aerosol of formulations described herein, injection of an aerosol of formulations described herein, or drops of a formulation described herein.

“Oral administration” or “orally” or “oral” is a route of administration where a substance (e.g. a pharmaceutical composition) is taken through the mouth. In some embodiments, when it is used without any further descriptors, it refers to administration of a substance through the mouth and directly into the gastrointestinal tract. Oral administration generally includes a number of forms, such as tablets, pills, capsules, and solutions.

02 May 2016

2012212269

The terms “oral inhalation administration” or “oral inhalation delivery” or “oral inhalation” refer to a method of giving to a mammal a dosage of a pirfenidone or pyridone analog (or salt thereof) compound formulation described herein, through the mouth for delivery and absorption of the formulation directly to the lungs of the mammal. In some
5 embodiments, oral inhalation administration is carried out by the use of a nebulizer.

The term “abnormal liver function” may manifest as abnormalities in levels of biomarkers of liver function, including alanine transaminase, aspartate transaminase, bilirubin, and/or alkaline phosphatase, and may be an indicator of drug-induced liver injury. See FDA Draft Guidance for Industry. Drug-Induced Liver Injury: Premarketing Clinical
10 Evaluation, October 2007.

"Grade 2 liver function abnormalities" include elevations in alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP), or gamma-glutamyl transferase (GGT) greater than 2.5-times and less than or equal to 5-times the upper limit of normal (ULN). Grade 2 liver function abnormalities also include elevations of bilirubin levels
15 greater than 1.5-times and less than or equal to 3-times the ULN.

“Gastrointestinal adverse events” include but are not limited to any one or more of the following: dyspepsia, nausea, diarrhea, gastroesophageal reflux disease (GERD) and vomiting.

A “carrier” or “excipient” is a compound or material used to facilitate administration
20 of the compound, for example, to increase the solubility of the compound. Solid carriers include, *e.g.*, starch, lactose, dicalcium phosphate, sucrose, and kaolin. Liquid carriers include, *e.g.*, sterile water, saline, buffers, non-ionic surfactants, and edible oils such as oil, peanut and sesame oils. In addition, various adjuvants such as are commonly used in the art may be included. These and other such compounds are described in the literature, *e.g.*, in the
25 Merck Index, Merck & Company, Rahway, NJ. Considerations for the inclusion of various components in pharmaceutical compositions are described, *e.g.*, in Gilman et al. (Eds.) (1990); Goodman and Gilman’s: The Pharmacological Basis of Therapeutics, 8th Ed., Pergamon Press.

A “diagnostic” as used herein is a compound, method, system, or device that assists in
30 the identification and characterization of a health or disease state. The diagnostic can be used in standard assays as is known in the art.

02 May 2016
2012212269

“Patient” or “subject” are used interchangeably and refer to a mammal.

The term “mammal” is used in its usual biological sense. In some embodiments, a mammal is a human.

The term “ex vivo” refers to experimentation or manipulation done in or on living tissue in an artificial environment outside the organism.

The term “pharmaceutically acceptable carrier” or “pharmaceutically acceptable excipient” includes any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents and the like. The use of such media and agents for pharmaceutically active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active ingredient, its use in the therapeutic compositions is contemplated. Supplementary active ingredients can also be incorporated into the compositions.

The term “pharmaceutically acceptable salt” refers to salts that retain the biological effectiveness and properties of the compounds of this invention and, which are not biologically or otherwise undesirable. In many cases, the compounds of this invention are capable of forming acid and/or base salts by virtue of the presence of amino and/or carboxyl groups or groups similar thereto. Pharmaceutically acceptable acid addition salts can be formed with inorganic acids and organic acids. Inorganic acids from which salts can be derived include, for example, hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like. Organic acids from which salts can be derived include, for example, acetic acid, propionic acid, naphtoic acid, oleic acid, palmitic acid, pamoic (emboic) acid, stearic acid, glycolic acid, pyruvic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, ascorbic acid, glucoheptonic acid, glucuronic acid, lactic acid, lactobioic acid, tartaric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid, and the like. Pharmaceutically acceptable base addition salts can be formed with inorganic and organic bases. Inorganic bases from which salts can be derived include, for example, sodium, potassium, lithium, ammonium, calcium, magnesium, iron, zinc, copper, manganese, aluminum, and the like; particularly preferred are the ammonium, potassium, sodium, calcium and magnesium salts. Organic bases from which salts can be derived include, for example, primary, secondary, and tertiary amines, substituted amines including naturally

02 May 2016

2012212269

occurring substituted amines, cyclic amines, basic ion exchange resins, and the like, specifically such as isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, histidine, arginine, lysine, benethamine, N-methyl-glucamine, and ethanolamine. Other acids include dodecylsulfuric acid, naphthalene-1,5-disulfonic acid, naphthalene-2-sulfonic acid, and saccharin.

The term “pH-reducing acid” refers to acids that retain the biological effectiveness and properties of the compounds of this invention and, which are not biologically or otherwise undesirable. Pharmaceutically acceptable pH-reducing acids include, for example, inorganic acids such as, *e.g.*, hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like. Also by nonlimiting example, pH-reducing acids may also include organic acids such as citric acid, acetic acid, propionic acid, naphthoic acid, oleic acid, palmitic acid, pantoic (emboic) acid, stearic acid, glycolic acid, pyruvic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, ascorbic acid, glucoheptonic acid, glucuronic acid, lactic acid, lactobioic acid, tartaric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid, and the like.

According to certain herein disclosed embodiments a pirfenidone or a pyridone analog compound formulation may comprise an “acidic excipient” that is typically present as an acidic excipient aqueous solution. Examples of may include acid salts such as phosphate, sulphate, nitrate, acetate, formate, citrate, tartrate, propionate and sorbate, organic acids such as carboxylic acids, sulfonic acids, phosphonic acids, phosphinic acids, phosphoric monoesters, and phosphoric diesters, and/or other organic acids that contain from 1 to 12 carbon atoms, citric acid, acetic acid, formic acid, propionic acid, butyric acid, benzoic acid, mono-, di-, and trichloroacetic acid, salicylic acid, trifluoroacetic acid, benzenesulfonic acid, toluenesulfonic acid, methylphosphonic acid, methylphosphinic acid, dimethylphosphinic acid, and phosphonic acid monobutyl ester.

A “buffer” refers to a compound that functions to regulate pH. In certain related embodiments the pH buffer is present under conditions and in sufficient quantity to maintain a pH that is “about” a recited pH value. “About” such a pH refers to the functional presence of that buffer, which, as is known in the art, may be a consequence of a variety of factors including pKa value(s) of the buffer, buffer concentration, working temperature, effects of

02 May 2016
2012212269

other components of the composition on pKa (*i.e.*, the pH at which the buffer is at equilibrium between protonated and deprotonated forms, typically the center of the effective buffering range of pH values), and other factors.

Hence, “about” in the context of pH may be understood to represent a quantitative variation in pH that may be more or less than the recited value by no more than 0.5 pH units, more preferably no more than 0.4 pH units, more preferably no more than 0.3 pH units, still more preferably no more than 0.2 pH units, and most preferably no more than 0.1-0.15 pH units. As also noted above, in certain embodiments a substantially constant pH (*e.g.*, a pH that is maintained within the recited range for an extended time period) may be from about pH 4.0 to about pH 8.0, from about pH 4.0 to about pH 7.0, or from about pH 4.0 to about pH 6.8, or any other pH or pH range as described herein, which in preferred embodiments may be from about pH 4.0 to about pH 8.0 for a pirfenidone or pyridone analog compound formulation, and greater than about pH 8.0 for a pirfenidone or pyridone analog compound aqueous solution.

Therefore the pH buffer typically may comprise a composition that, when present under appropriate conditions and in sufficient quantity, is capable of maintaining a desired pH level as may be selected by those familiar with the art, for example, buffers comprising citrate, formate, malate, formate, pyridine, piperazine, succinate, histidine, maleate, bis-Tris, pyrophosphate, PIPES, ACES, histidine, MES, cacodylic acid, H₂CO₃ / NaHCO₃ and N-(2-Acetamido)-2-iminodiacetic acid (ADA) or other buffers for maintaining, preserving, enhancing, protecting or otherwise promoting desired biological or pharmacological activity of a pirfenidone or pyridone analog compound, based on the disclosure herein. Suitable buffers may include those in Table 1 or known to the art (see, *e.g.*, Calbiochem® Biochemicals & Immunochemicals Catalog 2004/2005, pp. 68-69 and catalog pages cited therein, EMD Biosciences, La Jolla, CA).

Non-limiting examples of buffers that may be used according to certain embodiments disclosed herein, include but are not limited to formate (pKa 3.77), Citric acid (pKa₂ 4.76), Malate (pKa₂ 5.13), Pyridine (pKa 5.23), Piperazine ((pKa₁) 5.33), Succinate ((pKa₂) 5.64), Histidine (pKa 6.04), Maleate ((pKa₂) 6.24), Citric acid ((pKa₃) 6.40), Bis-Tris (pKa 6.46), Pyrophosphate ((pKa₃) 6.70), PIPES (pKa 6.76), ACES (pKa 6.78), Histidine (pKa 6.80), MES (pKa 6.15), Cacodylic acid (pKa 6.27), H₂CO₃ / NaHCO₃ (pKa₁) (6.37),

02 May 2016

2012212269

ADA (N-(2-Acetamido)-2-iminodiacetic acid) (pKa 6.60). In some embodiments, pharmaceutical compositions disclosed herein include a citrate buffer or a phosphate buffer. In some embodiments, pharmaceutical compositions disclosed herein include a citrate buffer. In some embodiments, pharmaceutical compositions disclosed herein include a phosphate
5 buffer.

“Solvate” refers to the compound formed by the interaction of a solvent and pirfenidone or a pyridone analog compound, a metabolite, or salt thereof. Suitable solvates are pharmaceutically acceptable solvates including hydrates.

By “therapeutically effective amount” or “pharmaceutically effective amount” is
10 meant pirfenidone or a pyridone analog compound, as disclosed for this invention, which has a therapeutic effect. The doses of pirfenidone or a pyridone analog compound which are useful in treatment are therapeutically effective amounts. Thus, as used herein, a therapeutically effective amount means those amounts of pirfenidone or a pyridone analog compound which produce the desired therapeutic effect as judged by clinical trial results
15 and/or model animal pulmonary fibrosis, cardiac fibrosis, kidney fibrosis, hepatic fibrosis, heart or kidney toxicity, multiple sclerosis, COPD or asthma. In particular embodiments, the pirfenidone or pyridone analog compounds are administered in a pre-determined dose, and thus a therapeutically effective amount would be an amount of the dose administered. This amount and the amount of the pirfenidone or pyridone analog compound can be routinely
20 determined by one of skill in the art, and will vary, depending on several factors, such as the therapeutic or prophylactic effect for fibrotic, inflammatory or demyelination injury occurs, and how distant that disease site is from the initial respiratory location receiving the initial inhaled aerosol dose. This amount can further depend upon the patient’s height, weight, sex, age and medical history. For prophylactic treatments, a therapeutically effective amount is
25 that amount which would be effective to prevent a fibrotic, inflammatory or demyelination injury.

A “therapeutic effect” relieves, to some extent, one or more of the symptoms associated with inflammation, fibrosis and/or demyelination. This includes slowing the progression of, or preventing or reducing additional inflammation, fibrosis and/or
30 demyelination. For IPF, a “therapeutic effect” is defined as a patient-reported improvement in quality of life and/or a statistically significant increase in or stabilization of exercise tolerance

02 May 2016
2012212269

and associated blood-oxygen saturation, reduced decline in baseline forced vital capacity, decreased incidence in acute exacerbations, increase in progression-free survival, increased time-to-death or disease progression, and/or reduced lung fibrosis. For cardiac fibrosis, a "therapeutic effect" is defined as a patient-reported improvement in quality of life and/or a statistically significant improvement in cardiac function, reduced fibrosis, reduced cardiac stiffness, reduced or reversed valvular stenosis, reduced incidence of arrhythmias and/or reduced atrial or ventricular remodeling. For kidney fibrosis, a "therapeutic effect" is defined as a patient-reported improvement in quality of life and/or a statistically significant improvement in glomerular filtration rate and associated markers. For hepatic fibrosis, a "therapeutic effect" is defined as a patient-reported improvement in quality of life and/or a statistically significant lowering of elevated aminotransferases (e.g., AST and ALT), alkaline phosphatases, gamma-glutamyl transferase, bilirubin, prothrombin time, globulins, as well as reversal of thrombocytopenia, leukopenia and neutropenia and coagulation defects. Further a potential reversal of imaging, endoscopic or other pathological findings. For COPD, a "therapeutic effect" is defined as a patient-reported improvement in quality of life and/or a statistically significant improved exercise capacity and associated blood-oxygen saturation, FEV1 and/or FVC, a slowed or halted progression in the same, progression-free survival, increased time-to-death or disease progression, and/or reduced incidence or acute exacerbation. For asthma, a "therapeutic effect" is defined as a patient-reported improvement in quality of life and/or a statistically significantly improved exercise capacity, improved FEV1 and/or FVC, and/or reduced incidence or acute exacerbation. For multiple sclerosis, a "therapeutic effect" is defined as a patient-reported improvement in quality of life and/or a statistically significantly improved Scripps Neurological Rating Scale score, improvement in bladder dysfunction, improved Disability Status Score, MRI lesion count, and/or an slowed or halted progression of disease.

"Treat," "treatment," or "treating," as used herein refers to administering a pharmaceutical composition for therapeutic purposes. In some embodiments, treating refers to alleviating, abating or ameliorating at least one symptom of a disease or condition, preventing any additional symptoms from arising, arresting the progression of at least one current symptom of the disease or condition, relieving at least one of the symptoms of a disease or condition, causing regression of the disease or condition, relieving a condition

2012212269 02 May 2016

caused by the disease or condition, or stopping the symptoms of the disease or condition. In some embodiments, the compositions described herein are used for prophylactic treatment. The term “prophylactic treatment” refers to treating a patient who is not yet diseased but who is susceptible to, or otherwise at risk of, a particular disease, or who is diseased but whose condition does not worsen while being treated with the pharmaceutical compositions described herein. The term “therapeutic treatment” refers to administering treatment to a patient already suffering from a disease. Thus, in preferred embodiments, treating is the administration to a mammal (either for therapeutic or prophylactic purposes) of therapeutically effective amounts of pirfenidone or a pyridone analog compound.

“Treat,” “treatment,” or “treating,” as used herein refers to administering a pharmaceutical composition for prophylactic and/or therapeutic purposes. The term “prophylactic treatment” refers to treating a patient who is not yet diseased, but who is susceptible to, or otherwise at risk of, a particular disease. The term “therapeutic treatment” refers to administering treatment to a patient already suffering from a disease. Thus, in preferred embodiments, treating is the administration to a mammal (either for therapeutic or prophylactic purposes) of therapeutically effective amounts of pirfenidone or a pyridone analog compound.

The term “dosing interval” refers to the time between administrations of the two sequential doses of a pharmaceutical’s during multiple dosing regimens.

The “respirable delivered dose” is the amount of aerosolized pirfenidone or a pyridone analog compound particles inhaled during the inspiratory phase of the breath simulator that is equal to or less than 5 microns.

“Lung Deposition” as used herein, refers to the fraction of the nominal dose of an active pharmaceutical ingredient (API) that is deposited on the inner surface of the lungs.

“Nominal dose,” or “loaded dose” refers to the amount of drug that is placed in the nebulizer prior to administration to a mammal. The volume of solution containing the nominal dose is referred to as the “fill volume.”

“Enhanced pharmacokinetic profile” means an improvement in some pharmacokinetic parameter. Pharmacokinetic parameters that may be improved include, AUC_{last} , $AUC_{(0-\infty)}$, T_{max} , and optionally a C_{max} . In some embodiments, the enhanced pharmacokinetic profile may be measured quantitatively by comparing a pharmacokinetic parameter obtained for a

02 May 2016
2012212269

nominal dose of an active pharmaceutical ingredient (API) administered with one type of inhalation device with the same pharmacokinetic parameter obtained with oral administration of a composition of the same active pharmaceutical ingredient (API).

"Blood plasma concentration" refers to the concentration of an active pharmaceutical ingredient (API) in the plasma component of blood of a subject or patient population.

"Respiratory condition," as used herein, refers to a disease or condition that is physically manifested in the respiratory tract, including, but not limited to, pulmonary fibrosis, chronic obstructive pulmonary disease (COPD), bronchitis, chronic bronchitis, emphysema, or asthma.

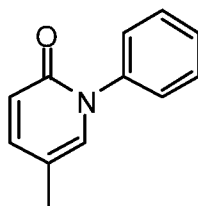
"Nebulizer," as used herein, refers to a device that turns medications, compositions, formulations, suspensions, and mixtures, etc. into a fine mist or aerosol for delivery to the lungs. Nebulizers may also be referred to as atomizers.

"Drug absorption" or simply "absorption" typically refers to the process of movement of drug from site of delivery of a drug across a barrier into a blood vessel or the site of action, e.g., a drug being absorbed in the pulmonary capillary beds of the alveoli.

Pirfenidone and Pyridone Analog Compounds

As also noted elsewhere herein, in preferred embodiments the pyridone compound for use in a pyridone compound formulation as described herein comprises pirfenidone (5-methyl-1-phenyl-2-(1H)-pyridone) or a salt thereof. Although various embodiments are described with the use of pirfenidone, it is noted that other pyridone analog compounds, or salts thereof, may be used in place of pirfenidone.

Pirfenidone is also known as 5-methyl-1-phenyl-2-(1H)-pyridone and has the structure:



"Pyridone analog" or "pyridone compound" refers to compounds that have the same type of biological activity and effectiveness as pirfenidone. Such pyridone analog compounds are those that upon administration to a mammal produce anti-inflammatory, anti-fibrotic and/or anti-demyelination activity for therapeutic or prophylactic purposes. In some

02 May 2016
2012212269

embodiments, a pyridone analog is a compound that has a substituted 2-(1H)pyridone or 3-(1H)pyridone core structure. In some embodiments, a pyridone analog is a compound that has a substituted 2-(1H)pyridone core structure.

1-Phenyl-2-(1H)pyridone, 5-methyl-1-(4-methylphenyl)-2-(1H)-pyridone, 5-methyl-1-(4-hydroxyphenyl)-2-(1H)-pyridone, 5-methyl-1-(4-methoxyphenyl)-2-(1H)-pyridone, 5-Methyl-1-(2'-pyridyl)-2-(1H)pyridone, 6-Methyl-1-phenyl-3-(1H)pyridone, 6-Methyl-1-phenyl-2-(1H)pyridone, 5-Methyl-1-p-tolyl-3-(1H)pyridone, 5-Methyl-3-phenyl-1-(2'-thienyl)-2-(1H)pyridone, 5-Methyl-1-(2'-naphthyl)-3-(1H)pyridone, 5-Methyl-1-(2'-naphthyl)-2-(1H)pyridone, 5-Methyl-1-phenyl-3-(1H)pyridone, 5-Methyl-1-p-tolyl-2-(1H)pyridone, 5-Methyl-1-(1'-naphthyl)-2-(1H)pyridone, 5-Methyl-1-(5'-quinolyl)-3-(1H)pyridone, 5-Ethyl-1-phenyl-2-(1H)pyridone, 5-Ethyl-1-phenyl-3-(1H)pyridone, 5-Methyl-1-(5'-quinolyl)-2-(1H)pyridone, 5-Methyl-1-(4'-methoxyphenyl)-3-(1H)pyridone, 5-Methyl-1-(4'-quinolyl)-2-(1H)pyridone, 4-Methyl-1-phenyl-3-(1H)pyridone, 5-Methyl-1-(4'-pyridyl)-2-(1H)pyridone, 5-Methyl-1-(3'-pyridyl)-3-(1H)pyridone, 3-Methyl-1-phenyl-2-(1H)pyridone, 5-Methyl-1-(4'-methoxyphenyl)-2-(1H)pyridone, 5-Methyl-1-(2'-Thienyl)-3-(1H)pyridone, 5-Methyl-1-(2'-pyridyl)-3-(1H)pyridone, 1,3-Diphenyl-2-(1H)pyridone, 1,3-Diphenyl-5-methyl-2-(1H)pyridone, 5-Methyl-1-(2'-quinolyl)-3-(1H)pyridone, 5-Methyl-1-(3'-trifluoromethylphenyl)-2-(1H)pyridone, 1-Phenyl-3-(1H)pyridone, 1-(2'-Furyl)-5-methyl-3-(1H)-pyridone, 3-Ethyl-1-phenyl-2-(1H)pyridone, 1-(4'-Chlorophenyl)-5-methyl-1-(1H)pyridone, 5-Methyl-1-(3'-pyridyl)-2-3-(1H)pyridone, 5-Methyl-1-(3-nitrophenyl)-2-(1H)pyridone, 3-(4'-Chlorophenyl)-5-Methyl-1-phenyl-2-(1H)pyridone, 5-Methyl-1-(2'-Thienyl)-2-(1H)pyridone, 5-Methyl-1-(2'-thiazolyl)-2-(1H)pyridone, 3,6-Dimethyl-1-phenyl-2-(1H)pyridone, 1-(4'Chlorophenyl)-5-Methyl-2-(1H)pyridone, 1-(2'-Imidazolyl)-5-Methyl-2-(1H)pyridone, 1-(4'-Nitrophenyl)-2-(1H)pyridone, 1-(2'-Furyl)-5-Methyl-2-(1H)pyridone, 1-Phenyl-3-(4'-chlorophenyl)-2-(1H)pyridone.

In some embodiments, a pyridone analog compound is a compound described in US patent publication no. US20090005424; US patent publication no. 20070092488; US Patent 8,022,087; US Patent 6,090,822; US Patent 5,716,632; US Patent 5,518,729; US Patent 5,310,562; US Patent 4,052,509; US Patent 4,042,699; US Patent 3,839,346; or US Patent 3,974,281.

02 May 2016
2012212269

In some embodiments, a pyridone analog is a deuterated pirfenidone compound, where 1 or more hydrogen atoms of pirfenidone are replaced with deuterium.

According to certain other distinct embodiments of the compositions and methods described herein, the pyridone compound is selected from the group consisting of bis(2-hydroxyethyl)azanum; 2-(3,5-diiodo-4-oxopyridin-1-yl)acetate, propyl 2-(3,5-diiodo-4-oxopyridin-1-yl)acetate, 2-[3-[4-(3-chlorophenyl)piperazin-1-yl]propyl] [1,2,4]triazolo[4,3-a]pyridin-3-one hydrochloride, 2-[3-[4-(3-chlorophenyl)piperazin-1-yl]propyl]-[1,2,4]triazolo[4,3-a]pyridin-3-one, 3-anilino-1-phenylpropan-1-one, 2-[3-[4-(3-chlorophenyl)piperazin-1-yl]propyl]-[1,2,4]triazolo[4,3-a]pyridin-3-one hydrochloride, 2-[3-[4-(3-chlorophenyl)piperazin-1-yl]propyl]-[1,2,4]triazolo[4,3-a]pyridin-3-one, 2S)-2-amino-3-(3-hydroxy-4-oxopyridin-1-yl)propanoic acid, 2-[3-[4-(3-chlorophenyl)piperazin-1-yl]propyl]-[1,2,4]triazolo[4,3-a]pyridin-3-one, 2-[3-[4-(3-chlorophenyl)piperazin-1-yl]propyl]-[1,2,4]triazolo[4,3-a]pyridin-3-one hydrochloride, 2-[3-[4-(3-chlorophenyl)piperazin-1-yl]propyl]-[1,2,4]triazolo[4,3-a]pyridin-3-one hydrochloride, (2S)-2-[(3-hydroxy-4-oxopyridin-1-yl)amino] propanoic acid, 2-[3-[4-(3-chlorophenyl)piperazin-1-yl]propyl]-[1,2,4]triazolo[4,3-a]pyridin-3-one hydrochloride, 2-amino-3-(3-hydroxy-4-oxopyridin-1-yl)propanoic acid, 2-[3-[4-(3-chlorophenyl)piperazin-1-yl]propyl]-[1,2,4]triazolo[4,3-a]pyridin-3-one hydrochloride, propyl 2-(3,5-diiodo-4-oxopyridin-1-yl)acetate, 2-(3,5-diiodo-4-oxopyridin-1-yl)acetic acid; 2-(2-hydroxyethylamino)ethanol, (2S)-2-amino-3-(3-hydroxy-4-oxopyridin-1-yl)propanoic acid, (2R)-2-amino-3-(3-hydroxy-4-oxopyridin-1-yl)propanoic acid, 2-amino-3-(3-hydroxy-4-oxopyridin-1-yl)propanoic acid, 5-cyano-6-methyl-N-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide, 6-methyl-N-[4-(methylsulfonyl)benzyl]-5-nitro-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide, 5-(1-butoxyvinyl)-6-methyl-N-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide, 5-acetyl-6-methyl-N-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide, 5-[(1E)-N-methoxyethanimidoyl]-6-methyl-N-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide, 5-[(1E)-N-hydroxyethanimidoyl]-6-methyl-N-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide, 6-methyl-N-[4-

02 May 2016
2012212269

(methanesulfonyl)benzyl]-2-oxo-5-(pyridin-3-yl ethynyl)-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide, 6-methyl-N-[4-(methanesulfonyl)benzyl]-2-oxo-5-(2-pyridin-3-ylethyl)-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide, 6-methyl-N-[4-(methanesulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-5-vinyl-1,2-dihydropyridine-3-carboxamide, ethyl 2-methyl-5-({[4(methanesulfonyl)benzyl]amino}carbonyl)-6-oxo-1-[3-(trifluoromethyl)phenyl]-1,6-dihydropyridine-3-carboxylate, 5-(4-methanesulfonyl-benzylcarbamoyl)-2-methyl-6-oxo-1-(3-trifluoromethyl-phenyl)-1,6-dihydropyridine-3-carboxylic acid, 6-methyl-2-oxo-1-(3-trifluoromethyl-phenyl)-1,2-dihydropyridine-3,5-dicarboxylic acid 5-dimethylamide 3-(4-methanesulfonyl-benzylamide), 6-methyl-2-oxo-1-(3-trifluoromethyl-phenyl)-1,2-dihydropyridine-3,5-dicarboxylic acid 5-amide 3-(4-methanesulfonyl-benzylamide), 6-methyl-2-oxo-1-(3-trifluoromethyl-phenyl)-1,2-dihydropyridine-3,5-dicarboxylic acid 3-(4-methanesulfonyl-benzylamide)5-methylamide, 6-methyl-2-oxo-1-(3-trifluoromethyl-phenyl)-1,2-dihydropyridine-3,5-dicarboxylic acid 5-[(2-hydroxy-ethyl)-methyl-amide]3-(4-methanesulfonyl-benzylamide), 6-methyl-2-oxo-1-(3-trifluoromethyl-phenyl)-1,2-dihydropyridine-3,5-dicarboxylic acid 3-(4-methanesulfonyl-benzylamide)5-(methyl-propyl-amide), 6-methyl-2-oxo-5-(pyrrolidine-1-carbonyl)-1-(3-trifluoromethyl-phenyl)-1,2-dihydropyridine-3,5-dicarboxylic acid 3-(4-methanesulfonyl-benzylamide), 6-methyl-2-oxo-1-(3-trifluoromethyl-phenyl)-1,2-dihydropyridine-3,5-dicarboxylic acid 5-[(2-dimethylamino-ethyl)-methyl-amide]3-(4-methanesulfonyl-benzylamide), 5-((2R)-2-hydroxymethyl-pyrrolidine-1-carbonyl)-6-methyl-2-oxo-1-(3-trifluoromethyl-phenyl)-1,2-dihydropyridine-3-carboxylic acid 3-(4-methanesulfonyl-benzylamide), 5-(3-hydroxy-pyrrolidine-1-carbonyl)-6-methyl-2-oxo-1-(3-trifluoromethyl-phenyl)-1,2-dihydropyridine-3,5-dicarboxylic acid 3-(4-methanesulfonyl-benzylamide), N³-[(1,1-dioxido-2,3-dihydro-1-benzothien-5-yl)methyl]-N⁵,N⁵,6-trimethyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3,5-dicarboxamide, 5-(N¹-acetyl-hydrazinocarbonyl)-6-methyl-2-oxo-1-(3-trifluoromethyl-phenyl)-1,2-dihydropyridine-3-carboxylic acid 4-methanesulfonyl-benzylamide, 5-[N¹-(2-cyano-acetyl)-hydrazinocarbonyl]-6-methyl-2-oxo-1-(3-trifluoromethyl-phenyl)-1,2-dihydropyridine-3-carboxylic acid 4-methanesulfonyl-benzylamide, 5-{[2-(aminocarbonothioyl)hydrazino]carbonyl}-6-methyl-N-[4-(methanesulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide, 5-hydrazinocarbonyl-6-

02 May 2016
2012212269

5 methyl-2-oxo-1-(3-trifluoromethyl-phen yl)-1,2-dihydro-pyridine -3-carboxylic acid 4-
methanesulfonyl-benzylamide, 5-({2-[(ethylamino)carbonyl]hydrazino}carbonyl)-6-methyl-
N-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-
carboxamide, 5-({2-[(N,N-dimethylamino)carbonyl]hydrazino}carbonyl)-6-methyl-N-[4-
10 (methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-
carboxamide, 5-(3,3-dimethyl-ureido)-6-methyl-2-oxo-1-(3-trifluoromethyl- phenyl)-1,2-
dihydro-pyridine -3-carboxylic acid 4-methanesulfonyl-benzylamide, 6-methyl-5-(3-methyl-
ureido)-2-oxo-1-(3-trifluoromethyl-phen yl)-1,2-dihydro-pyridine-3-carboxylic acid 4-
methanesulfonyl-benzylamide, 6-methyl-2-oxo-1-(3-trifluoromethyl-phenyl)-5-ureido-1,2-
15 dihydro-pyridine-3-carboxylic acid 4-methanesulfonyl-benzylamide, 5-amino-6-methyl-2-
oxo-1-(3-trifluoromethyl-phenyl)-1,2-dihydro-pyridine-3-carboxylic acid 4-
methanesulfonyl-benzylamide, 6-methyl-N-[4-(methylsulfonyl)benzyl]-2-oxo-5-propionyl-1-
[3 -(trifluoromethyl) phenyl]-1,2-dihydropyridine-3-carboxamide, 5-formyl-6-methyl-N-[4-
(methyl sulfonyl)benzyl]-2-oxo-1-[3-(t rifluoromethyl)phenyl]-1,2-dihydropyridine-3-
20 carboxamide, 6-methyl-N-[4-(methylsulfonyl)benzyl]-2-oxo-5-(3-oxobutyl)-1 -[3-
(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide, 5-acetyl-N-[4-
(isopropylsulfonyl)benzyl]-6-methyl-2-oxo-1-[3 -(trifluoromethyl)phenyl]-1,2-
dihydropyridine-3-carboxamide, 5-acetyl-1-(3-cyano-phenyl)-6-methyl-2-oxo-1,2-dihydro-
pyrid ine-3-carboxylic acid 4-methanesulfonyl-benzylamide, 5-acetyl-1-(3-chloro-phenyl)-6-
25 methyl-2-oxo-1,2-dihydro-pyridine-3-carboxylic acid 4-methanesulfonyl-benzylamide, 5-
acetyl-6-methyl-2-oxo-1-m-tolyl-1,2-dihydro-pyridine-3-carboxylic acid 4-methanesulfonyl-
benzylamide, 5-(1-hydroxyethyl)-6-methyl-N-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-
(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide, 5-(1-azidoethyl)-6-methyl-N-
[4-(methylsulfonyl) benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-
30 carboxamide, 6-methyl-N-[4-(methylsulfonyl)benzyl]-5-(1-morpholin-4-yleth yl)-2-oxo-1-[3-
(trifluoromethyl)phenyl]-1,2-dihydropyridine- 3-carboxamide, 5-(1-hydroxypropyl)-6-
methyl-N-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-
dihydropyridine-3-carb oxamide, 5-(1-hydroxyethyl)-N-[4-(isopropylsulfonyl) benzyl]-6-
methyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide, N-[4-
(cyclopropylsulfonyl)benzyl]-5-formyl-6-methyl-2-oxo 1-[3-(trifluoromethyl)phenyl]-1,2-
dihydropyridine-3-carboxamide, 5-[(E)-(methoxyimino) methyl]-6-methyl-N-[4-

02 May 2016
2012212269

- (methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide, 5-(hydroxymethyl)-6-methyl-N-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide, 5-[(dimethylamino)methyl]-6-methyl-N-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide, 6-methyl-5-[(methylamino)methyl]-N-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide, 6-methyl-N-[4-(methylsulfonyl)benzyl]-5-(morpholin-4-ylmethyl)-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide, 5-[(2-furylmethyl)amino]methyl}-6-methyl-N-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide, 5-[(cyclopropylamino)methyl]-6-methyl-N-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide, 5-[(2-hydroxypropyl)amino]methyl}-6-methyl-N-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide, 5-[(cyclopentylamino)methyl]-6-methyl-N-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide, 5-[(2-hydroxyethyl)(methyl)amino]methyl}-6-methyl-N-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide, 6-methyl-N-[4-(methylsulfonyl)benzyl]-2-oxo-5-(pyrrolidin-1-ylmethyl)-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide, 5-[(methoxy(methyl)amino)methyl]-6-methyl-N-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide, 5-[(cyanomethyl)amino]methyl}-6-methyl-N-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide, 5-[(cyclopropylmethyl)amino]methyl}-6-methyl-N-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide, 5-[(3-hydroxypyrrolidin-1-yl)methyl]-6-methyl-N-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide, 5-(2-hydroxyethoxy)-N-[4-(isopropylsulfonyl)benzyl]-6-methyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide, 2-methyl-5-[(4-(methylsulfonyl)benzyl)amino]carbonyl)-6-oxo-1-[3-(trifluoromethyl)phenyl]-1,6-dihydropyridine-3-yl acetate, 5-methoxy-6-methyl-N-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide, 5-(3-methoxypropoxy)-6-

02 May 2016
2012212269

methyl-N-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-
 dihydropyridine-3-carboxamide, 2-methyl-5-({[4-(methylsulfonyl)benzyl]amino}carbonyl)-
 6-oxo-1-[3-(trifluoromethyl)phenyl]-1,6-dihydropyridine-3-yl methanesulfonate, 5-ethoxy-6-
 methyl-N-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-
 5 dihydropyridine-3-carboxamide, 5-(2-hydroxyethoxy)-6-methyl-N-[4-
 (methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-
 carboxamide, 5-(cyanomethoxy)-6-methyl-N-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-
 (trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide, 2-({2-methyl-5-({[4-
 (methylsulfonyl)benzyl]amino}carbonyl)-6-oxo-1-[3-(trifluoromethyl)phenyl]-1,6-
 10 dihydropyridine-3-yl}oxy)ethyl acetate, 5-[2-(dimethylamino)-2-oxoethoxy]-6-methyl-N-[4-
 (methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-
 carboxamide, 5-(2-aminoethoxy)-N-[4-(isopropylsulfonyl)benzyl]-6-methyl-2-oxo-1-[3-
 (trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide, 5-(acetylamino)-6-methyl-N-
 [4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-
 15 carboxamide, N-[4-(isopropylsulfonyl)benzyl]-6-methyl-5-[3-(methylamino)propoxy]-2-
 oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide, 5-(1-methoxyethyl)-
 6-methyl-N-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-
 dihydropyridine-3-carboxamide, 5-(2-bromo-1-methoxyethyl)-6-methyl-N-[4-
 (methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-
 20 carboxamide, 5-(1-isopropoxyethyl)-6-methyl-N-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-
 (trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide, 5-(N¹-isobutyryl-
 hydrazinocarbonyl)-6-methyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-
 carboxylic acid 4-methanesulfonyl-benzylamide, N⁵-methoxy-6-methyl-N³-[4-
 (methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3,5-
 25 dicarboxamide, N⁵-methoxy-N⁵,6-dimethyl-N³-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-
 (trifluoromethyl)phenyl]-1,2-dihydropyridine-3,5-dicarboxamide, 5-[(2,5-dimethyl-2,5-
 dihydro-1H-pyrrol-1-yl)carbonyl]-6-methyl-N-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-
 (trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide, 6-methyl-N³-[4-
 (methylsulfonyl)benzyl]-2-oxo-N⁵-pyrrolidin-1-yl-1-[3-(trifluoromethyl)phenyl]-1,2-dih-
 30 ydropyridine-3,5-dicarboxamide, 6-methyl-N-[4-(methylsulfonyl)benzyl]-2-oxo-5-(piperidin-
 1-ylcarbonyl)-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide, 6-methyl-

02 May 2016
2012212269

5 N³-[4-(methylsulfonyl) benzyl]-N⁵-morpholin-4-yl-2-oxo-1-[3-(trifluoromethyl) phenyl]-1,2-dihydro pyridine-3,5-dicarboxamide, 6-methyl-5-[(4-methylpiperidin-1-yl)carbonyl]-N-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide, 6-methyl-N³-[4-(methylsulfonyl)benzyl]-2-oxo-N⁵-piperidin-1-yl-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3,5-dicarboxamide, N⁵-(tert-butyl)-N⁵,6-dimethyl-N³-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3,5-dicarboxamide, N⁵-butyl-N⁵,6-dimethyl-N³-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3,5-dicarboxamide, N⁵-ethyl-N⁵-isopropyl-6-methyl-N³-[4-(methylsulfonyl) benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3,5-dicarboxamide, 5-[N¹-(formylhydrazinocarbonyl)-6-methyl-2-oxo-1-(3-trifluoromethyl-phenyl)-1,2-dihydro-pyridine-3-carboxylic acid 4-methanesulfonyl-benzylamide, N¹-[5-(4-methanesulfonyl-benzylcarbamoyl)-2-methyl-6-oxo-1-(3-trifluoromethyl-phenyl) -1,6-dihydro-pyridine-3-carbonyl]-hydrazinecarboxylic acid ethyl ester, 5-({2-[(ethylamino)carbonothioyl]hydrazino}carbonyl)-6-methyl-N-[4-(methylsulfonyl) benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide, 5-(isoxazolidin-2-ylcarbonyl)-6-methyl-N-[4-(methylsulfonyl) benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide, 6-methyl-2-oxo-1-(3-trifluoromethyl-phenyl)-1,2-dihydropyridine-3,5-dicarboxylic acid 5-(methoxy-methyl-amide)3-[4-(propane-2-sulfonyl)-benzylamide], 6-methyl-2-oxo-1-(3-trifluoromethyl-phenyl)-1,2-dihydro-pyridine-3,5-dicarboxylic acid 3-(4-ethanesulfonyl-benzylamide)5-(methoxy-methyl-amide), 6-methyl-2-oxo-1-(3-trifluoromethyl-phenyl)-1,2-dihydro-pyridine-3,5-dicarboxylic acid 3-(4-cyclopropanesulfonyl-benzylamide)5-(methoxy-methyl-amide), 6-methyl-2-oxo-1-(3-trifluoromethyl-phenyl)-1,2-dihydro-pyridine-3,5-dicarboxylic acid 5-[(2-hydroxy-ethyl)-amide]3-(4-methanesulfonyl-benzylamide, 5-(isoxazolidine-2-carbonyl)-6-methyl-2-oxo-1-(3-trifluoromethyl-phenyl)1,2-dihydro-pyridine -3-carboxylic acid 4-ethanesulfonyl-benzylamide, 5-(isoxazolidine-2-carbonyl)-6-methyl-2-oxo-1-(3-trifluoromethylphenyl)1,2-dihydropyridine-3-carboxylic acid 4-cyclopropane sulfonylbenzylamide, 5-(N-hydroxycarbamimidoyl)-6-methyl-2-oxo-1-(3-trifluoromethyl-phenyl)-1,2-dihydro-pyridine-3-carboxylic acid 4-methanesulfonyl-benzylamide, N³-(cyclohexylmethyl)-N⁵,N⁵,6-trimethyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3,5-dicarboxamide, N⁵

02 May 2016
2012212269

,N⁵,6-trimethyl-2-oxo-N³-(pyridin-3-ylmethyl)-1-[3-(trifluoromethyl)-phenyl]-1,2-dihydropyridine-3,5-dicarboxamide, N⁵,N⁵,6-trimethyl-N³-(2-morpholin-4-ylethyl)-2-oxo-1-[3-(trifluoromethyl)-phenyl]-1,2-dihydropyridine-3,5-dicarboxamide, N⁵,N⁵,6-trimethyl-N³-(3-morpholin-4-ylpropyl)-2-oxo-1-[3-(trifluoromethyl)-phenyl]-1,2-dihydropyridine-3,5-dicarboxamide, N³-benzyl-N⁵,N⁵,6-trimethyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydro-pyridine-3,5-dicarboxamide, N³-[2-(1H-indol-3-yl)ethyl]-N⁵,N⁵,6-trimethyl-2-oxo-1-[3-(trifluoromethyl)-phenyl]-1,2-dihydro pyridine-3,5-dicarboxamide, N⁵,N⁵,6-trimethyl-2-oxo-N³-(1-phenylethyl)-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3,5-dicarboxamide, N⁵,N⁵,6-trimethyl-2-oxo-N³-(2-phenylethyl)-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3,5-dicarboxamide, N⁵,N⁵,6-trimethyl-2-oxo-N³-[(2R)-2-phenylcyclopropyl]-1-[3-(trifluoromethyl)-phenyl]-1,2-dihydropyridine-3,5-dicarboxamide, N³-(2,3-dihydro-1H-inden-2-yl)-N⁵,N⁵,6-trimethyl-2-oxo-1-[3-(trifluoromethyl)-phenyl]-1,2-dihydropyridine-3,5-dicarboxamide, N³-[2-(1,3-benzodioxol-5-yl)ethyl]-N⁵,N⁵,6-trimethyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3,5-dicarboxamide, 5-{[4-(2-hydroxyethyl)piperazin-1-yl]carbonyl}-N,N,2-trimethyl-6-oxo-1-[3-(trifluoromethyl)phenyl]-1,6-dihydropyridine-3-carboxamide, N³-(1-ethylpyrrolidin-2-yl)methyl-N⁵,N⁵,6-trimethyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3,5-dicarboxamide, N⁵,N⁵,6-trimethyl-N³-[3-(2-methylpiperidin-1-yl)propyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3,5-dicarboxamide, N⁵,N⁵,6-trimethyl-N³-(1-naphthylmethyl)-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3,5-dicarboxamide, N³-(1,3-benzodioxol-5-ylmethyl)-N⁵,N⁵,6-trimethyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3,5-dicarboxamide, N³-(3,4-difluorobenzyl)-N⁵,N⁵,6-trimethyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3,5-dicarboxamide, N³-(2-chloro-4-fluorobenzyl)-N⁵,N⁵,6-trimethyl-2-oxo-1-[3-(trifluoromethyl)-phenyl]-1,2-dihydropyridine-3,5-dicarboxamide, N⁵,N⁵,6-trimethyl-2-oxo-N³-(2-thienylmethyl)-1-[3-(trifluoromethyl)phenyl]-1,2-dihydro pyridine-3,5-dicarboxamide, N³-(3,4-dichlorobenzyl)-N⁵,N⁵,6-trimethyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3,5-dicarboxamide, N³-[2-(2,4-dichlorophenyl)ethyl]-N⁵,N⁵,6-trimethyl-2-oxo-1-[3-(trifluoromethyl)-phenyl]-1,2-dihydropyridine-3,5-dicarboxamide, N³-(2-cyclohex-1-en-1-ylethyl)-N⁵,N⁵,6-trimethyl-2-oxo-1-[3-(trifluoromethyl)-phenyl]-1,2-dihydropyridine-3,5-dicarboxamide, N³-[1-(4-

02 May 2016
2012212269

chlorophenyl)ethyl]-N⁵,N⁵,6-trimethyl-2-oxo-1-[3-(trifluoromethyl)-phenyl]-1,2-
dihydropyridine-3,5-dicarboxamide, N⁵,N⁵,6-trimethyl-2-oxo-N³-[3-(2-oxopyrrolidin-1-
yl)propyl]-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3,5-dicarboxamide, N⁵,N⁵,6-
trimethyl-2-oxo-N³-(pyridin-4-ylmethyl)-1-[3-(trifluoromethyl)phenyl]-1, 2-
5 dihydropyridine-3,5-dicarboxamide, N,N,2-trimethyl-6-oxo-5-[(4-phenyl)piperazin-1-
yl)carbonyl]-1-[3-(trifluoromethyl)phenyl]-1,6-dihydropyridine-3-carboxamide, N,N,2-
trimethyl-6-oxo-5-[(4-pyridin-2-yl)piperazin-1-yl)carbonyl]-1-[3-(trifluoromethyl)phenyl]-
1,6-dihydropyridine-3-carboxamide, N³-(2,3-dihydro-1-benzofuran-5-ylmethyl)-N⁵,N⁵,6-
trimethyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3,5-dicarboxamide,
10 methyl 4-[(5-[(dimethylamino)carbonyl]-6-methyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-
1,2-dihydropyridin-3-yl)carbonyl)amino]methyl} benzoate, 5-{[3-(dimethylamino)
pyrrolidin-1-yl]carbonyl}-N,N,2-trimethyl-6-oxo-1-[3-(trifluoromethyl)phenyl]-1,6-
dihydropyridine-3-carboxamide, N⁵,N⁵,6-trimethyl-2-oxo-N³-[2-(2-thienyl)ethyl]-1-[3-
(trifluoromethyl)phenyl]-1, 2-dihydropyridine-3,5-dicarboxamide, N⁵,N⁵,6-trimethyl-2-
15 oxo-N³-(4-phenoxybenzyl)-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3,5-
dicarboxamide, N⁵,N⁵,6-trimethyl-2-oxo-N³-(3-thienylmethyl)-1-[3-
(trifluoromethyl)phenyl]-1,2-dihydropyridine-3,5-dicarboxamide, N³-[2-(4-tert-
butylphenyl)ethyl]-N⁵,N⁵,6-trimethyl-2-oxo-1-[3-(trifluoromethyl)-phenyl]-1,2-
dihydropyridine-3,5-dicarboxamide, N³-{2-[4-(aminosulfonyl)phenyl]ethyl}-N⁵,N⁵,6-
20 trimethyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3,5-dicarboxamide, N⁵
,N⁵,6-trimethyl-2-oxo-N³-[4-(1H-pyrazol-1-yl)benzyl]-1-[3-(trifluoromethyl)-phenyl]-1,2-
dihydropyridine-3,5-dicarboxamide, N⁵,N⁵,6-trimethyl-2-oxo-N³-phenoxy-1-[3-
(trifluoromethyl)phenyl]-1,2-dihydro-pyridine-3,5-dicarboxamide, N³-(2,3-dihydro-1,4-
benzodioxin-2-ylmethyl)-N⁵,N⁵,6-trimethyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-d
25 ihydropyridine-3,5-dicarboxamide, N³-[(6-fluoro-4H-1,3-benzodioxin-8-yl)methyl]-N⁵,N⁵
,6-trimethyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3,5-dicarboxamide, N³-
(1-benzothien-3-ylmethyl)-N⁵,N⁵,6-trimethyl-2-oxo-1-[3-(trifluoromethyl)-phenyl]-1,2-
dihydropyridine-3,5-dicarboxamide, N⁵,N⁵,6-trimethyl-2-oxo-N³-[2-(tetrahydro-2H-
pyran-4-yl)ethyl]-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3,5-dicarboxamide, N⁵
30 ,N⁵,6-trimethyl-N³-[(1-methyl-1H-pyrazol-4-yl)methyl]-2-oxo-1-[3-(triflu
oromethyl)phenyl]-1,2-dihydropyridine-3,5-dicarboxamide, N⁵,N⁵,6-trimethyl-2-oxo-N³-

02 May 2016
2012212269

[(1-phenyl-1H-pyrazol-4-yl)methyl]-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3,5-dicarboxamide, N³ -[(5-methoxy-4-oxo-4H-pyran-2-yl)methyl]-N⁵,N⁵,6-trimethyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3,5-dicarboxamide, N³ -(3-azepan-1-ylpropyl)-N⁵,N⁵,6-trimethyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3,5-dicarboxamide, N³ -(4-cyanobenzyl)-N⁵,N⁵,6-trimethyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3,5-dicarboxamide, N⁵,N⁵,6-trimethyl-2-oxo-N³ -[3-(5-oxo-4,5-dihydro-1H-pyrazol-4-yl)propyl]-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3,5-dicarboxamide, N³ -{[(2R)-1-ethylpyrrolidin-2-yl]methyl}-N⁵,N⁵,6-trimethyl-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3,5-dicarboxamide, 5-cyclopropyl-6-methyl-N-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide, 6-methyl-5-(2-methyl-1,3-dioxolan-2-yl)-N-[4-(methylsulfonyl)benzyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide, 5-(4,5-dihydro-oxazol-2-yl)-6-methyl-2-oxo-1-(3-trifluoromethyl-phenyl)-1,2-dihydro-pyridine-3-carboxylic acid 4-methanesulfonyl-benzylamide, 5-cyclopropyl-6-methyl-N-{[5-(methylsulfonyl)pyridin-2-yl]methyl}-2-oxo-1-[3-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxamide, 2-amino-3-(3-hydroxy-4-oxopyridin-1-yl)propanoic acid, (2S)-2-amino-3-(3-hydroxy-4-oxopyridin-1-yl)propanoic acid, 2-amino-3-(3-hydroxy-4-oxopyridin-1-yl)propanoic acid, (2S)-2-amino-3-(3-hydroxy-4-oxopyridin-1-yl)propanoic acid, 2-amino-3-(3-hydroxy-4-oxopyridin-1-yl)propanoic acid, 2-amino-3-(3-hydroxy-4-oxopyridin-1-yl)propanoic acid, 2-amino-3-(3-hydroxy-4-oxopyridin-1-yl)propanoic acid, propyl 2-(3,5-diiodo-4-oxopyridin-1-yl)acetate, (2S)-2-azaniumyl-3-(3-hydroxy-4-oxopyridin-1-yl)propanoate, propyl 2-(3,5-diiodo-4-oxopyridin-1-yl)acetate, 2-(4-aminophenyl)ethanol, 4-hydroxy-5-(3-methylanilino)-1H-pyrimidin-6-one, 6-cyclohexyl-1-hydroxy-4-methylpyridin-2-one, 1,6-dimethyl-2-oxo-5-pyridin-4-ylpyridine-3-carbonitrile, (2-oxo-1H-pyridin-3-yl) acetate, 3-methyl-1-(2,4,6-trimethylphenyl)butan-1-one, 5-methyl-1-phenylpyridin-2-one, 6-cyclohexyl-1-hydroxy-4-methylpyridin-2-one, 2-aminoethanol; 6-cyclohexyl-1-hydroxy-4-methylpyridin-2-one, 4-[(3,5-diiodo-4-oxopyridin-1-yl)methyl]benzoic acid, 2-aminoethanol; 3-[(6-hydroxy-5-methyl-2-oxo-1H-pyridin-3-yl)imino]-5-methylpyridine-2,6-dione, 5-ethyl-3-[(5-ethyl-2-methoxy-6-methylpyridin-3-yl)methylamino]-6-methyl-1H-pyridin-2-one, 6-cyclohexyl-1-hydroxy-4-methyl pyridin-2-one, 5-(2,5-dihydroxyphenyl)-1H-pyridin-2-one, 6-(4,4-dimethyl-5-oxofuran-2-yl)-1H-

2012212269 02 May 2016

pyridin-2-one, N'-(6-oxo-1H-pyridin-2-yl)-N,N-dipropyl methanimidamide, [6-oxo-1-
 [(2R,3R,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxyl methyl)oxan-2-yl]pyridin-2-yl]acetic acid,
 5 5-(2,5-dihydroxyphenyl)-1H-pyridin-2-one, 3-[(6-hydroxy-5-methyl-2-oxo-1H-pyridin-3-
 yl)imino]-5-methylpyridine-2,6 -dione, 5-(4-cyanophenyl)-6-methyl-2-oxo-1H-pyridine-3-
 carbonitrile, 3,3-diethyl-1-[(piperazin-1-ylamino)methyl]pyridine-2,4-dione, 5-ethyl-3-[(5-
 ethyl-2-methoxy-6-methylpyridin-3-yl)methylamino]-6-methyl-1H-pyridin-2-one and
 pharmaceutically acceptable salts thereof.

In some embodiments, the pirfendione or pyridone analog compound is used in
 compositions and methods described herein in free-base or free-acid form. In other
 10 embodiments, the pirfendione or pyridone analog compound is used as pharmaceutically
 acceptable salts. In some embodiments, pharmaceutically acceptable salts are obtained by
 reacting the compound with an acid or with a base. The type of pharmaceutical acceptable
 salts, include, but are not limited to: (1) acid addition salts, formed by reacting the free base
 form of the compound with a pharmaceutically acceptable: (1) acid such as, for example,
 15 hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, metaphosphoric acid,
 acetic acid, propionic acid, hexanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic
 acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid,
 trifluoroacetic acid, tartaric acid, citric acid, benzoic acid, 3-(4-hydroxybenzoyl)benzoic acid,
 cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, 1,2-
 20 ethanedisulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, toluenesulfonic
 acid, 2-naphthalenesulfonic acid, 4-methylbicyclo-[2.2.2]oct-2-ene-1-carboxylic acid,
 glucoheptonic acid, 4,4'-methylenebis-(3-hydroxy-2-ene-1-carboxylic acid), 3-
 phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, lauryl sulfuric acid,
 gluconic acid, glutamic acid, hydroxynaphthoic acid, salicylic acid, stearic acid, muconic
 25 acid, butyric acid, phenylacetic acid, phenylbutyric acid, valproic acid, and the like; or (2)
 base, where an acidic proton present in the parent compound is replaced by a metal ion, e.g.,
 an alkali metal ion (e.g. lithium, sodium, potassium), an alkaline earth ion (e.g. magnesium,
 or calcium), or an aluminum ion. In some cases, the pirfendione or pyridone analog
 compound is reacted with an organic base, such as, but not limited to, ethanolamine,
 30 diethanolamine, triethanolamine, tromethamine, N-methylglucamine, dicyclohexylamine,

tris(hydroxymethyl)methylamine or with an amino acid such as, but not limited to, arginine, lysine, and the like.

Advantages of Inhaled Aerosol and Topical (Non-Oral) Drug Delivery

Inhalation therapy of aerosolized pirfenidone or a pyridone analog compound enables direct deposition of the sustained-release or active substance in the respiratory tract (be that intra-nasal or pulmonary) for therapeutic action at that site of deposition or systemic absorption to regions immediately down stream of the vascular absorption site. In the case of central nervous system (CNS) deposition, intra-nasal inhalation aerosol delivery deposits pirfenidone or a pyridone analog compound directly upstream of the CNS compartment.

Similar to the intra-nasal and pulmonary applications described above, treatment or prevention of organs outside the respiratory tract requires absorption to the systemic vascular department for transport to these extra-respiratory sites. In the case of treating or preventing fibrotic or inflammatory diseases associated with the heart, liver and kidney, deposition of drug in the respiratory tract, more specifically the deep lung will enable direct access to these organs through the left atrium to either the carotid arteries or coronary arteries. Similarly, in the case of treating CNS disorder (e.g., multiple sclerosis), deposition of drug in the respiratory tract (as defined above) or nasal cavity, more specifically the absorption from the nasal cavity to the nasal capillary beds for immediate access to the brain and CNS. This direct delivery will permit direct dosing of high concentration pirfenidone or a pyridone analog compound in the absence of unnecessary systemic exposure. Similarly, this route permits titration of the dose to a level that may be critical for these indications.

Pharmaceutical Compositions

For purposes of the method described herein, a pyridone analog compound, most preferably pirfenidone may be administered using a liquid nebulization, dry powder or metered-dose inhaler. In some embodiments, pirfenidone or a pyridone analog compound disclosed herein is produced as a pharmaceutical composition suitable for aerosol formation, dose for indication, deposition location, pulmonary or intra-nasal delivery for pulmonary, intranasal/sinus, or extra-respiratory therapeutic action, good taste, manufacturing and storage stability, and patient safety and tolerability.

In some embodiments, the isoform content of the manufactured pyridone analog compound, most preferably pirfenidone may be optimized for drug substance and drug

product stability, dissolution (in the case of dry powder or suspension formulations) in the nose and/or lung, tolerability, and site of action (be that lung, nasal/sinus, or regional tissue).

Manufacture

In some embodiments, pirfenidone drug product (DP) includes pirfenidone at a concentration of about 1 mg/mL to about 100 mg/mL in aqueous buffer (citrate or phosphate pH = 4 to 8), plus optional added salts (NaCl and/or MgCl₂ and/or MgSO₄). In some embodiments, the pirfenidone drug product also includes co-solvent(s) (by non-limiting example ethanol, propylene glycol, and glycerin) and/or surfactant(s) (by non-limiting example Tween 80, Tween 60, lecithin, Cetylpyridinium, and Tween 20). In some embodiments, the formulation also includes a taste-masking agent (by non-limiting example sodium saccharin).

To achieve pirfenidone concentrations above 3 mg/mL, manufacturing process are described. In one embodiment, the manufacturing process includes high temperature pirfenidone aqueous dissolution, followed by co-solvent and/or surfactant and/or salt addition, and subsequent cooling to ambient temperature. In this process, added co-solvent and/or surfactant and/or salt stabilize the high-temperature-dissolved pirfenidone during the cooling process and provide a stable, high-concentration, ambient-temperature formulation of pirfenidone. In some embodiments, the processing temperature is 30°C, 35°C, 40°C, 45°C, 50°C, 55°C, 60°C, 65°C, 70°C, 75°C, 80°C, 85°C, 90°C, 95°C, 100°C or other pressure-enabled increased temperature. In some embodiments, the process includes addition of surfactant and/or co-solvent and/or salt at the highest temperature or incrementally-lower temperature as the solution is cooled. In some embodiments, addition of surfactant and/or co-solvent and/or salt occurs all at once or incrementally during a maintained temperature or as the solution is cooled. The time by which the solution is maintained at the highest temperature is from 0 minutes to 24 hours. The time by which the solution is cooled from the highest temperature is from 0 minutes to 24 hours. In some embodiments, the solution is protected from light. In some embodiments, the solution is sparged to remove or lower the oxygen concentration. In some embodiments, the head space of the reaction container includes an inert gas or mixture of inert gases. Inert gases include, but are not limited to, nitrogen and argon. In some embodiments, the pirfenidone drug product includes co-solvent(s) in the concentration range of 0% to 100% in otherwise buffered aqueous solution.

02 May 2016
2012212269

In some embodiments, the pirfenidone drug product includes co-solvent(s) at a concentration of about 1% to about 25%. Co-solvents include, but are not limited to, ethanol, glycerin or propylene glycol. In some embodiments, the pirfenidone drug product includes surfactant(s) in the concentration range of 0% to 100% in otherwise buffered aqueous solution. In some
5 embodiments, the pirfenidone drug product includes surfactant(s) at a concentration of about 0.1% to about 10%. Surfactants include, but are not limited to Tween 20, Tween 60, Tween 80, Cetylpyridinium Bromide, or Lecithin. In some embodiments, the pirfenidone drug product includes a buffer. In some embodiments, the buffer includes salt and/or acid forms of agents such as citrate, phosphate or formate at a concentration between 0 mM to 1000 mM.
10 In some embodiments, the buffer includes salt and/or acid forms of agents such as citrate, phosphate or formate at a concentration between about 1 mM and about 50 mM. In some embodiments, the pirfenidone drug product includes a salt. In some embodiments, the salt is present at a concentration between 0% to 100%. In some embodiments, the salt is present at a concentration between about 0.1% and about 5%. In some embodiments, the salt is sodium
15 chloride, magnesium chloride, magnesium sulfate or barium chloride. In some embodiments, a sweetening agent is added to the pirfenidone drug product. In some embodiments, the sweetening agent is saccharin or a salt thereof. In some embodiments, the sweetening agent is present at a concentration between about 0.01 mM and about 10 mM. In some
embodiments, the pH of the buffered solution will be between about 2.0 and about 10.0.

20 In another embodiment, the manufacturing process includes excess co-solvent and/or surfactant and/or cation addition to a super-saturated pirfenidone aqueous solution. Upon dissolution in the excess co-solvent and/or surfactant and/or cation aqueous solution, the formulation is diluted to reduce co-solvent and/or surfactant and/or cation concentrations to within the concentration range generally-recognized as safe and/or non-toxic and/or non-
25 irritable.

In some embodiments, the manufacturing process is as described in Example 5.

Administration

The pyridone analog compound, most preferably pirfenidone as disclosed herein can be administered at a therapeutically effective dosage, *e.g.*, a dosage sufficient to provide
30 treatment for the disease states previously described. Generally, for example, a daily aerosol

02 May 2016
2012212269

dose of pirfenidone in a pirfenidone compound formulation may be from about 0.001 mg to about 6.6 mg pirfenidone/kg of body weight per dose. Thus, for administration to a 70 kg person, the dosage range would be about 0.07 mg to about 463 mg pirfenidone per dose or up to about 0.280 mg to about 1852 mg pirfenidone day. The amount of active compound administered will, of course, be dependent on the subject and disease state being treated, the severity of the affliction, the manner and schedule of administration, the location of the disease (*e.g.*, whether it is desired to effect intra-nasal or upper airway delivery, pharyngeal or laryngeal delivery, bronchial delivery, pulmonary delivery and/or pulmonary delivery with subsequent systemic or central nervous system absorption), and the judgment of the prescribing physician; for example, a likely dose range for aerosol administration of pirfenidone in preferred embodiments, or in other embodiments of pyridone analog compound, would be about 0.28 to 1852 mg per day.

Another unexpected observation is that inhalation delivery of aerosol pirfenidone to the lung exhibits less metabolism of pirfenidone observed with oral administration. Thus, oral or intranasal inhalation of pirfenidone or pyridone analog will permit maximum levels of active substance to the pulmonary tissue in the absence of substantial metabolism to inactive agents.

Inhibitors of CYP enzymes reduce pirfenidone metabolism resulting in elevated blood levels and associated toxicity. As many products effecting CYP enzymes are useful to fibrosis patients, permitting their use would be beneficial. While the oral route is already at the maximum permissible dose (which provides only moderate efficacy), any inhibition of the enzymes described above elevates pirfenidone blood levels and increases the rate and severity of the toxic events described herein. Because oral and intranasal inhalation delivery of pirfenidone or pyridone analogs can achieve effective tissue levels with much less drug than that required by the oral product, resulting blood levels are significantly lower and consequences associated with CYP enzyme inhibitory properties described herein are removed. Thus, permitting use of these CYP inhibitory enzyme products currently contraindicated with the oral medicine.

The primary metabolite of pirfenidone is 5-carboxy-pirfenidone. Following oral or intravenous administration, this metabolite appears quickly at high concentrations in blood. 5-carboxy-pirfenidone does not appear to have anti-fibrotic or anti-inflammatory activity, its

02 May 2016

2012212269

high blood levels occur at the loss of pirfenidone blood concentrations. Thus, while the oral product is dosed at the highest possible level, once pirfenidone enters the blood it is rapidly metabolized to a non-active species further reducing the drugs potential to achieve sufficient lung levels required for substantital efficacy. Because oral and intranasal inhalation delivery of pirfenidone or pyridone analogs can achieve effective lung tissue levels directly extra-lung metabolism is not a factor.

Administration of the pyridone analog compound, most preferably pirfenidone as disclosed herein, such as a pharmaceutically acceptable salt thereof, can be via any of the accepted modes of administration for agents that serve similar utilities including, but not limited to, aerosol inhalation such as nasal and/or oral inhalation of a mist or spray containing liquid particles, for example, as delivered by a nebulizer.

Pharmaceutically acceptable compositions thus may include solid, semi-solid, liquid and aerosol dosage forms, such as, *e.g.*, powders, liquids, suspensions, complexations, liposomes, particulates, or the like. Preferably, the compositions are provided in unit dosage forms suitable for single administration of a precise dose. The unit dosage form can also be assembled and packaged together to provide a patient with a weekly or monthly supply and can also incorporate other compounds such as saline, taste masking agents, pharmaceutical excipients, and other active ingredients or carriers.

The pyridone analog compound, most preferably pirfenidone as disclosed herein, such as a pharmaceutically acceptable salt thereof, can be administered either alone or more typically in combination with a conventional pharmaceutical carrier, excipient or the like (*e.g.*, mannitol, lactose, starch, magnesium stearate, sodium saccharin, talcum, cellulose, sodium crosscarmellose, glucose, gelatin, sucrose, magnesium carbonate, magnesium chloride, magnesium sulfate, calcium chloride, lactose, sucrose, glucose and the like). If desired, the pharmaceutical composition can also contain minor amounts of nontoxic auxiliary substances such as wetting agents, emulsifying agents, solubilizing agents, pH buffering agents and the like (*e.g.*, citric acid, ascorbic acid, sodium phosphate, potassium phosphate, sodium acetate, sodium citrate, cyclodextrin derivatives, sorbitan monolaurate, triethanolamine acetate, triethanolamine oleate, and the like). Generally, depending on the intended mode of administration, the pharmaceutical formulation will contain about 0.005% to 95%, preferably about 0.1% to 50% by weight of a compound of the invention. Actual

02 May 2016
2012212269

methods of preparing such dosage forms are known, or will be apparent, to those skilled in this art; for example, see Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton, Pennsylvania.

In one preferred embodiment, the compositions will take the form of a unit dosage form such as vial containing a liquid, solid to be suspended, dry powder, lyophilisate, or other composition and thus the composition may contain, along with the active ingredient, a diluent such as lactose, sucrose, dicalcium phosphate, or the like; a lubricant such as magnesium stearate or the like; and a binder such as starch, gum acacia, polyvinylpyrrolidone, gelatin, cellulose, cellulose derivatives or the like.

Liquid pharmaceutically administrable compositions can, for example, be prepared by dissolving, dispersing, etc. an active compound as defined above and optional pharmaceutical adjuvants in a carrier (*e.g.*, water, saline, aqueous dextrose, glycerol, glycols, ethanol or the like) to form a solution or suspension. Solutions to be aerosolized can be prepared in conventional forms, either as liquid solutions or suspensions, as emulsions, or in solid forms suitable for dissolution or suspension in liquid prior to aerosol production and inhalation. The percentage of active compound contained in such aerosol compositions is highly dependent on the specific nature thereof, as well as the activity of the compound and the needs of the subject. However, percentages of active ingredient of 0.01% to 90% in solution are employable, and will be higher if the composition is a solid, which will be subsequently diluted to the above percentages. In some embodiments, the composition will comprise 0.25%-50.0% of the active agent in solution.

Pirfenidone or pyridone analog compound formulations can be separated into two groups; those of simple formulation and complex formulations providing taste-masking for improved tolerability, pH-optimized for stability and tolerability, immediate or sustained-release, and/or area-under-the-curve (AUC) shape-enhancing properties. Simple formulations can be further separated into three groups. 1. Simple formulations may include water-based liquid formulations for nebulization. By non-limiting example water-based liquid formulations may consist of pirfenidone or pyridone analog compound alone or with non-encapsulating water soluble excipients. 2. Simple formulations may also include organic-based liquid formulations for nebulization or meter-dose inhaler. By non-limiting example organic-based liquid formulations may consist of pirfenidone or pyridone analog

02 May 2016

2012212269

compound or with non-encapsulating organic soluble excipients. 3. Simple formulations may also include dry powder formulations for administration with a dry powder inhaler. By non-limiting example dry powder formulations may consist of pirfenidone or pyridone analog compound alone or with either water soluble or organic soluble non-encapsulating excipients

5 with or without a blending agent such as lactose. Complex formulations can be further separated into five groups. 1. Complex formulations may include water-based liquid formulations for nebulization. By non-limiting example water-based liquid complex formulations may consist of pirfenidone or pyridone analog compound encapsulated or complexed with water-soluble excipients such as lipids, liposomes, cyclodextrins,

10 microencapsulations, and emulsions. 2. Complex formulations may also include organic-based liquid formulations for nebulization or meter-dose inhaler. By non-limiting example organic-based liquid complex formulations may consist of pirfenidone or pyridone analog compound encapsulated or complexed with organic-soluble excipients such as lipids, microencapsulations, and reverse-phase water-based emulsions. 3. Complex formulations

15 may also include low-solubility, water-based liquid formulations for nebulization. By non-limiting example low-solubility, water-based liquid complex formulations may consist of pirfenidone or pyridone analog compound as a low-water soluble, stable nanosuspension alone or in co-crystal/co-precipitate excipient complexes, or mixtures with low solubility lipids, such as lipid nanosuspensions. 4. Complex formulations may also include low-

20 solubility, organic-based liquid formulations for nebulization or meter-dose inhaler. By non-limiting example low-solubility, organic-based liquid complex formulations may consist of pirfenidone or pyridone analog compound as a low-organic soluble, stable nanosuspension alone or in co-crystal/co-precipitate excipient complexes, or mixtures with low solubility lipids, such as lipid nanosuspensions. 5. Complex formulations may also include dry powder

25 formulations for administration using a dry powder inhaler. By non-limiting example, complex dry powder formulations may consist of pirfenidone or pyridone analog compound in co-crystal/co-precipitate/spray dried complex or mixture with low-water soluble excipients/salts in dry powder form with or without a blending agent such as lactose. Specific methods for simple and complex formulation preparation are described herein.

30

02 May 2016
2012212269**Aerosol Delivery**

Pirfenidone or pyridone analog compounds as described herein are preferably directly administered as an aerosol to a site of pulmonary pathology including pulmonary fibrosis, COPD or asthma. The aerosol may also be delivered to the pulmonary compartment for absorption into the pulmonary vasculature for therapy or prophylaxis of extra-pulmonary pathologies such as fibrosis and inflammatory diseases of the heart, kidney and liver, or pulmonary or intra-nasal delivery for extra-pulmonary or extra-nasal cavity demyelination diseases associated with the central nervous system.

Several device technologies exist to deliver either dry powder or liquid aerosolized products. Dry powder formulations generally require less time for drug administration, yet longer and more expensive development efforts. Conversely, liquid formulations have historically suffered from longer administration times, yet have the advantage of shorter and less expensive development efforts. Pirfenidone or pyridone analog compounds disclosed herein range in solubility, are generally stable and have a range of tastes. In one such embodiment, pirfenidone or pyridone analog compounds are water soluble at pH 4 to pH 8, are stable in aqueous solution and have limited to no taste. Such a pyridone includes pirfenidone.

Accordingly, in one embodiment, a particular formulation of the pirfenidone or pyridone analog compound disclosed herein is combined with a particular aerosolizing device to provide an aerosol for inhalation that is optimized for maximum drug deposition at a site of infection, pulmonary arterial hypertension, pulmonary or intra-nasal site for systemic absorption for extra-nasal and/or extra-pulmonary indications, and maximal tolerability. Factors that can be optimized include solution or solid particle formulation, rate of delivery, and particle size and distribution produced by the aerosolizing device.

Particle Size and Distribution

The distribution of aerosol particle/droplet size can be expressed in terms of either:

- the mass median aerodynamic diameter (MMAD) — the droplet size at which half of the mass of the aerosol is contained in smaller droplets and half in larger droplets;
- volumetric mean diameter (VMD);
- mass median diameter (MMD);

02 May 2016
2012212269

- the fine particle fraction (FPF) —the percentage of particles that are $<5\text{ }\mu\text{m}$ in diameter.

These measures have been used for comparisons of the in vitro performance of different inhaler device and drug combinations. In general, the higher the fine particle
5 fraction, the higher the proportion of the emitted dose that is likely to deposit the lung.

Generally, inhaled particles are subject to deposition by one of two mechanisms: impaction, which usually predominates for larger particles, and sedimentation, which is prevalent for smaller particles. Impaction occurs when the momentum of an inhaled particle is large enough that the particle does not follow the air stream and encounters a physiological
10 surface. In contrast, sedimentation occurs primarily in the deep lung when very small particles which have traveled with the inhaled air stream encounter physiological surfaces as a result of random diffusion within the air stream.

For pulmonary administration, the upper airways are avoided in favor of the middle and lower airways. Pulmonary drug delivery may be accomplished by inhalation of an
15 aerosol through the mouth and throat. Particles having a mass median aerodynamic diameter (MMAD) of greater than about 5 microns generally do not reach the lung; instead, they tend to impact the back of the throat and are swallowed and possibly orally absorbed. Particles having diameters of about 1 to about 5 microns are small enough to reach the upper- to mid-pulmonary region (conducting airways), but are too large to reach the alveoli. Smaller
20 particles, *i.e.*, about 0.5 to about 2 microns, are capable of reaching the alveolar region. Particles having diameters smaller than about 0.5 microns can also be deposited in the alveolar region by sedimentation, although very small particles may be exhaled. Measures of particle size can be referred to as volumetric mean diameter (VMD), mass median diameter (MMD), or MMAD. These measurements may be made by impaction (MMD and MMAD)
25 or by laser (VMD). For liquid particles, VMD, MMD and MMAD may be the same if environmental conditions are maintained, *e.g.*, standard humidity. However, if humidity is not maintained, MMD and MMAD determinations will be smaller than VMD due to dehydration during impaction measurements. For the purposes of this description, VMD, MMD and MMAD measurements are considered to be under standard conditions such that
30 descriptions of VMD, MMD and MMAD will be comparable. Similarly, dry powder particle size determinations in MMD and MMAD are also considered comparable.

02 May 2016
2012212269

In some embodiments, the particle size of the aerosol is optimized to maximize the pirfenidone or pyridone analog compound deposition at the site of pulmonary pathology and/or extra-pulmonary, systemic or central nervous system distribution, and to maximize tolerability (or in the later case, systemic absorption). Aerosol particle size may be expressed in terms of the mass median aerodynamic diameter (MMAD). Large particles (*e.g.*, MMAD >5 μm) may deposit in the upper airway because they are too large to navigate the curvature of the upper airway. Small particles (*e.g.*, MMAD < 2 μm) may be poorly deposited in the lower airways and thus become exhaled, providing additional opportunity for upper airway deposition. Hence, intolerability (*e.g.*, cough and bronchospasm) may occur from upper airway deposition from both inhalation impaction of large particles and settling of small particles during repeated inhalation and expiration. Thus, in one embodiment, an optimum particle size is used (*e.g.*, MMAD = 2-5 μm) in order to maximize deposition at a mid-lung and to minimize intolerability associated with upper airway deposition. Moreover, generation of a defined particle size with limited geometric standard deviation (GSD) may optimize deposition and tolerability. Narrow GSD limits the number of particles outside the desired MMAD size range. In one embodiment, an aerosol containing one or more compounds disclosed herein is provided having a MMAD from about 2 microns to about 5 microns with a GSD of less than or equal to about 2.5 microns. In another embodiment, an aerosol having an MMAD from about 2.8 microns to about 4.3 microns with a GSD less than or equal to 2 microns is provided. In another embodiment, an aerosol having an MMAD from about 2.5 microns to about 4.5 microns with a GSD less than or equal to 1.8 microns is provided.

In some embodiments, the pirfenidone or pyridone analog compound that is intended for respiratory delivery (for either systemic or local distribution) can be administered as aqueous formulations, as suspensions or solutions in halogenated hydrocarbon propellants, or as dry powders. Aqueous formulations may be aerosolized by liquid nebulizers employing either hydraulic or ultrasonic atomization. Propellant-based systems may use suitable pressurized metered-dose inhalers (pMDIs). Dry powders may use dry powder inhaler devices (DPIs), which are capable of dispersing the drug substance effectively. A desired particle size and distribution may be obtained by choosing an appropriate device.

02 May 2016
2012212269

Lung Deposition as used herein, refers to the fraction of the nominal dose of an active pharmaceutical ingredient (API) that is bioavailable at a specific site of pharmacologic activity upon administration of the agent to a patient via a specific delivery route. For example, a lung deposition of 30% means 30% of the active ingredient in the inhalation device just prior to administration is deposited in the lung. Likewise, a lung deposition of 60% means 60% of the active ingredient in the inhalation device just prior to administration is deposited in the lung, and so forth. Lung deposition can be determined using methods of scintigraphy or deconvolution. In some embodiments, the present invention provides for methods and inhalation systems for the treatment or prophylaxis of a respiratory condition in a patient, comprising administering to the patient a nominal dose of pirfenidone or a pyridone analog compound with a liquid nebulizer. In some embodiments, the liquid nebulizer is a high efficiency liquid nebulizer. In some embodiments a lung deposition of pirfenidone or a pyridone analog compound of at least about 7%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, or at least about 85%, based on the nominal dose of pirfenidone or a pyridone analog compound is achieved.

There are two main methods used to measure aerosol deposition in the lungs. First, γ -scintigraphy is performed by radiolabeling the drug with a substance like 99m-technetium, and scanning the subject after inhalation of the drug. This technique has the advantage of being able to quantify the proportion of aerosol inhaled by the patient, as well as regional distribution in the upper airway and lungs. Second, since most of the drug deposited in the lower airways will be absorbed into the bloodstream, pharmacokinetic techniques are used to measure lung deposition. This technique can assess the total amount of ICSs that interacts with the airway epithelium and is absorbed systemically, but will miss the small portion that may be expectorated or swallowed after mucociliary clearance, and cannot tell us about regional distribution. Therefore, γ -scintigraphy and pharmacokinetic studies are in many cases considered complementary.

In some embodiments, administration of the pirfenidone or pyridone analog compound with a liquid nebulizer provides a GSD of emitted droplet size distribution of about 1.0 μm to about 2.5 μm , about 1.2 μm to about 2.0 μm , or about 1.0 μm to about 2.0

02 May 2016
2012212269

µm. In some embodiments, the MMAD is about 0.5µm to about 5 µm, or about 1 to about 4 µm or less than about 5 µm. In some embodiments, the VMD is about 0.5µm to about 5 µm, or about 1 to about 4 µm or less than about 5 µm.

Fine Particle Fraction (FPF) describes the efficiency of a nebulizer inhalation device.

5 FPF represents the percentage of the delivered aerosol dose, or inhaled mass, with droplets of diameter less than 5.0 µm. Droplets of less than 5.0 µm in diameter are considered to penetrate to the lung. In some embodiments, administration of an aqueous inhalation pirfenidone or pyridone analog solution with a liquid nebulizer provides a RDD of at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at
10 least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, or at least about 80%.

The Delivered Dose (DD) of drug to a patient is the certain portion of volume of liquid filled into the nebulizer, i.e. the fill volume, which is emitted from the mouthpiece of the device. The difference between the nominal dose and the DD is the amount of volume
15 lost primarily to residues, i.e. the amount of fill volume remaining in the nebulizer after administration, or is lost in aerosol form during expiration of air from the patient and therefore not deposited in the patient's body. In some embodiments, the DD of the nebulized formulations described herein is at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 60%, at least about
20 65%, at least about 70%, or at least about 80%.

The Respirable Delivered Dose (RDD) is an expression of the delivered mass of drug contained within emitted droplets from a nebulizer that are small enough to reach and deposit on the surface epithelium of the patients lung. The RDD is determined by multiplying the DD by the FPF.

25 In one embodiment, described herein an aqueous droplet containing pirfenidone or pyridone analog compound, wherein the aqueous droplet has a diameter less than about 5.0 µm. In some embodiments, the aqueous droplet has a diameter less than about 5.0 µm, less than about 4.5 µm, less than about 4.0 µm, less than about 3.5 µm, less than about 3.0 µm, less than about 2.5 µm, less than about 2.0 µm, less than about 1.5 µm, or less than about 1.0
30 µm. In some embodiments, the aqueous droplet further comprises one or more cosolvents. In some embodiments, the one or more cosolvents are selected from ethanol and propylene

02 May 2016
2012212269

glycol. In some embodiments, the aqueous droplet further comprises a buffer. In some
embodiments, the buffer is a citrate buffer or a phosphate buffer. In some embodiments, the
droplet was produced from a liquid nebulizer and an aqueous solution of pirfenidone or
pyridone analog compound as described herein. In some embodiments, the aqueous droplet
5 was produced from an aqueous solution that has concentration of pirfenidone or pyridone
analog compound between about 0.1 mg/mL and about 60 mg/mL and an osmolality from
about 50 mOsmol/kg to about 6000 mOsmol/kg. In some embodiments, the osmolality is
greater than about 100 mOsmol/kg. In some embodiments, the osmolality is greater than
about 400 mOsmol/kg. In some embodiments, the osmolality is greater than about 1000
10 mOsmol/kg. In some embodiments, the osmolality is greater than about 2000 mOsmol/kg.
In some embodiments, the osmolality is greater than about 3000 mOsmol/kg. In some
embodiments, the osmolality is greater than about 4000 mOsmol/kg. In some embodiments,
the osmolality is greater than about 5000 mOsmol/kg.

Also described are aqueous aerosols comprising a plurality of aqueous droplets of
15 pirfenidone or pyridone analog compound as described herein. In some embodiments, the at
least about 30% of the aqueous droplets in the aerosol have a diameter less than about 5 μ m.
In some embodiments, at least about 35%, at least about 40%, at least about 45%, at least
about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at
least about 75%, at least about 80%, at least about 85%, or at least about 90% of the aqueous
20 droplets in the aerosol have a diameter less than about 5 μ m. In some embodiments, the
aqueous aerosols are produced with a liquid nebulizer. In some embodiments, the aqueous
aerosols are produced with a high efficiency liquid nebulizer.

Liquid Nebulizer

In one embodiment, a nebulizer is selected on the basis of allowing the formation of
25 an aerosol of a pirfenidone or pyridone analog compound disclosed herein having an MMAD
predominantly between about 1 to about 5 microns. In one embodiment, the delivered
amount of pirfenidone or pyridone analog compound provides a therapeutic effect for
pulmonary pathology and/or extra-pulmonary, systemic, tissue or central nervous system
distribution.

30 Previously, two types of nebulizers, jet and ultrasonic, have been shown to be able to
produce and deliver aerosol particles having sizes between 2 and 4 micron. These particle

02 May 2016
2012212269

sizes have been shown as being optimal for middle airway deposition. However, unless a specially formulated solution is used, these nebulizers typically need larger volumes to administer sufficient amount of drug to obtain a therapeutic effect. A jet nebulizer utilizes air pressure breakage of an aqueous solution into aerosol droplets. An ultrasonic nebulizer
5 utilizes shearing of the aqueous solution by a piezoelectric crystal. Typically, however, the jet nebulizers are only about 10% efficient under clinical conditions, while the ultrasonic nebulizer is only about 5% efficient. The amount of pharmaceutical deposited and absorbed in the lungs is thus a fraction of the 10% in spite of the large amounts of the drug placed in the nebulizer. The amount of drug that is placed in the nebulizer prior to administration to
10 the mammal is generally referred to the “nominal dose,” or “loaded dose.” The volume of solution containing the nominal dose is referred to as the “fill volume.” Smaller particle sizes or slow inhalation rates permit deep lung deposition. Both middle-lung and alveolar deposition may be desired for this invention depending on the indication, *e.g.*, middle and/or alveolar deposition for pulmonary fibrosis and systemic delivery. Exemplary disclosure of
15 compositions and methods for formulation delivery using nebulizers can be found in, *e.g.*, US 2006/0276483, including descriptions of techniques, protocols and characterization of aerosolized mist delivery using a vibrating mesh nebulizer.

Accordingly, in one embodiment, a vibrating mesh nebulizer is used to deliver in preferred embodiments an aerosol of the pirfenidone compound as disclosed herein, or in
20 other embodiments, a pyridone analog compound as disclosed herein. A vibrating mesh nebulizer comprises a liquid storage container in fluid contact with a diaphragm and inhalation and exhalation valves. In one embodiment, about 1 to about 6 ml of the pirfenidone compound formulation (or in another related embodiment, of a pyridone analog compound formulation) is placed in the storage container and the aerosol generator is
25 engaged producing atomized aerosol of particle sizes selectively between about 1 and about 5 micron. In one embodiment, about 1 to about 10 mL of the pirfenidone compound formulation (or in another related embodiment, of a pyridone analog compound formulation) is placed in the storage container and the aerosol generator is engaged producing atomized aerosol of particle sizes selectively between about 1 and about 5 micron. In one embodiment,
30 about the volume of the pirfenidone compound formulation (or in another related

02 May 2016
2012212269

embodiment, of a pyridone analog compound formulation) that is originally placed in the storage container and the aerosol generator is replaced to increase the administered dose size.

In some embodiments a pirfenidone or pyridone analog compound formulation as disclosed herein, is placed in a liquid nebulization inhaler and prepared in dosages to deliver
5 from about 34 mcg to about 463 mg from a dosing solution of about 0.5 to about 6 ml with MMAD particles sizes between about 1 to about 5 micron being produced.

In some embodiments a pirfenidone or pyridone analog compound formulation as disclosed herein, is placed in a liquid nebulization inhaler and prepared in dosages to deliver
10 from about 34 mcg to about 463 mg from a dosing solution of about 0.5 to about 7 ml with MMAD particles sizes between about 1 to about 5 micron being produced.

By non-limiting example, a nebulized pirfenidone or pyridone analog compound may be administered in the described respirable delivered dose in less than about 20 min, less than about 15 min, less than about 10 min, less than about 7 min, less than about 5 min, less than about 3 min, or less than about 2 min.

15 By non-limiting example, a nebulized pirfenidone or pyridone analog compound may be administered in the described respirable delivered dose using a breath-actuated nebulizer in less than about 20 min, less than about 10 min, less than about 7 min, less than about 5 min, less than about 3 min, or less than about 2 min.

By non-limiting example, in other circumstances, a nebulized pirfenidone or pyridone
20 analog compound may achieve improved tolerability and/or exhibit an area-under-the-curve (AUC) shape-enhancing characteristic when administered over longer periods of time. Under these conditions, the described respirable delivered dose in more than about 2 min, preferably more than about 3 min, more preferably more than about 5 min, more preferably more than about 7 min, more preferably more than about 10 min, and in some cases most preferable
25 from about 10 to about 20 min.

As disclosed herein, there is provided a pyridone analog compound formulation composition comprising a pirfenidone compound aqueous solution having a pH from about 4.0 to about pH 8.0 where the pirfenidone compound is present at a concentration from about 34 mcg/mL to about 463 mg/mL pirfenidone. In certain other embodiments the pirfenidone
30 compound formulation is provided as an aqueous solution having a pH of from about 4.0 to about 8.0, the solution comprising a pirfenidone compound at a concentration of from about

02 May 2016
2012212269

34 mcg/mL to about 463 mg/mL pirfenidone; and citrate buffer or phosphate buffer at a concentration of from about 0 mM to about 50 mM. In certain other embodiments the pirfenidone compound formulation is provided as an aqueous solution having a pH of from about 4.0 to about 8.0, the solution comprising a pirfenidone compound at a concentration of
5 from about 34 mcg/mL to about 463 mg/mL pirfenidone; and a buffer that has a pKa between 4.7 and 6.8 and that is present at a concentration sufficient to maintain or maintain after titration with acid or base a pH from about 4.0 to about 8.0 for a time period sufficient to enable marketable product shelf-life storage.

In some embodiments, described herein is a pharmaceutical composition that
10 includes: pirfenidone; water; phosphate buffer or citrate buffer; and optionally sodium chloride or magnesium chloride. In other embodiments, described herein is a pharmaceutical composition that includes: pirfenidone; water; a buffer; and at least one additional ingredient selected from sodium chloride, magnesium chloride, ethanol, propylene glycol, glycerol, polysorbate 80, and cetylpyridinium bromide (or chloride). In some embodiments, the buffer
15 is phosphate buffer. In other embodiments, the buffer is citrate buffer. In some embodiments, the pharmaceutical composition includes 1 mg to 500 mg of pirfenidone, for example, 5 mg, 10 mg, 15 mg, 25 mg, 37.5 mg, 75 mg, 100 mg, 115 mg, 150 mg, 190 mg, 220 mg, or 500 mg. In some embodiments, the osmolality of the pharmaceutical composition described herein is between about 50 mOsmo/kg to 6000 mOsmo/kg. In some embodiments,
20 the osmolality of the pharmaceutical composition described herein is between about 50 mOsmo/kg to 5000 mOsmo/kg. In some embodiments, the pharmaceutical composition optionally includes saccharin (e.g. sodium salt). In some embodiments, such a pharmaceutical composition is placed in a liquid nebulization inhaler to deliver from about 1 mg to about 500 mg from a dosing solution of about 0.5 to about 6 mL with MMAD particles sizes between
25 about 1 to about 5 micron being produced. In some embodiments, such a pharmaceutical composition is placed in a liquid nebulization inhaler to deliver from about 1 mg to about 500 mg from a dosing solution of about 0.5 to about 7 mL with MMAD particles sizes between about 1 to about 5 micron being produced. In some embodiments such a nebulized pharmaceutical composition may deliver between about 0.0001 mg and about 25 mg
30 pirfenidone or pyridone analog in aerosol particles with a MMAD between 1 and 5 microns in each inhaled breath. In some embodiments, 1 mg pirfenidone or pyridone analog delivered

02 May 2016
2012212269

in 10 breaths over 1 minute, whereby 50% of the inhaled particles are between 1 and 5 microns, 0.05 mg pirfenidone or pyridine analog will be delivered in each breath. In some embodiments, 1 mg pirfenidone or pyridone analog delivered in 15 breaths per minute over 10 minutes, whereby 50% of the inhaled particles are between 1 and 5 microns, 0.0033 mg pirfenidone or pyridone analog will be delivered in each breath. In some embodiments, 1 mg pirfenidone or pyridone analog delivered in 20 breaths per minute over 20 minutes, whereby 50% of the inhaled particles are between 1 and 5 microns, 0.00125 mg pirfenidone or pyridone analog will be delivered in each breath. In some embodiments, 200 mg pirfenidone or pyridone analog delivered in 10 breaths over 1 minute, whereby 50% of the inhaled particles are between 1 and 5 microns, 10 mg pirfenidone or pyridone analog will be delivered in each breath. In some embodiments, 200 mg pirfenidone or pyridone analog delivered in 15 breaths per minute over 10 minutes, whereby 50% of the inhaled particles are between 1 and 5 microns, 0.67 mg pirfenidone or pyridone analog will be delivered in each breath. By another non-limiting example, In some embodiments, 200 mg pirfenidone or pyridone analog delivered in 20 breaths per minute over 20 minutes, whereby 50% of the inhaled particles are between 1 and 5 microns, 0.25 mg pirfenidone or pyridone analog will be delivered in each breath. In some embodiments, 500 mg pirfenidone or pyridine analog delivered in 10 breaths over 1 minute, whereby 50% of the inhaled particles are between 1 and 5 microns, 25 mg pirfenidone or pyridone analog will be delivered in each breath. In some embodiments, 500 mg pirfenidone or pyridone analog delivered in 15 breaths per minute over 10 minutes, whereby 50% of the inhaled particles are between 1 and 5 microns, 1.67 mg pirfenidone or pyridone analog will be delivered in each breath. In some embodiments, 500 mg pirfenidone or pyridone analog delivered in 20 breaths per minute over 20 minutes, whereby 50% of the inhaled particles are between 1 and 5 microns, 0.625 mg pirfenidone or pyridone analog will be delivered in each breath.

In some embodiments, a nebulized pirfenidone or pyridone analog compound may be administered in the described respirable delivered dose in less than about 20 min, less than about 10 min, less than about 7 min, less than about 5 min, less than about 3 min, or less than about 2 min.

For aqueous and other non-pressurized liquid systems, a variety of nebulizers (including small volume nebulizers) are available to aerosolize the formulations.

02 May 2016
2012212269

Compressor-driven nebulizers incorporate jet technology and use compressed air to generate the liquid aerosol. Such devices are commercially available from, for example, Healthdyne Technologies, Inc.; Invacare, Inc.; Mountain Medical Equipment, Inc.; Pari Respiratory, Inc.; Mada Medical, Inc.; Puritan-Bennet; Schuco, Inc., DeVilbiss Health Care, Inc.; and Hospitak, Inc. Ultrasonic nebulizers rely on mechanical energy in the form of vibration of a piezoelectric crystal to generate respirable liquid droplets and are commercially available from, for example, Omron Healthcare, Inc., Boehringer Ingelheim, and DeVilbiss Health Care, Inc. Vibrating mesh nebulizers rely upon either piezoelectric or mechanical pulses to respirable liquid droplets generate. Other examples of nebulizers for use with pirfenidone or pyridone analogs described herein are described in U.S. Patent Nos. 4,268,460; 4,253,468; 4,046,146; 3,826,255; 4,649,911; 4,510,929; 4,624,251; 5,164,740; 5,586,550; 5,758,637; 6,644,304; 6,338,443; 5,906,202; 5,934,272; 5,960,792; 5,971,951; 6,070,575; 6,192,876; 6,230,706; 6,349,719; 6,367,470; 6,543,442; 6,584,971; 6,601,581; 4,263,907; 5,709,202; 5,823,179; 6,192,876; 6,644,304; 5,549,102; 6,083,922; 6,161,536; 6,264,922; 6,557,549; and 6,612,303 all of which are hereby incorporated by reference in their entirety.

Any known inhalation nebulizer suitable to provide delivery of a medicament as described herein may be used in the various embodiments and methods described herein. Such nebulizers include, e.g., jet nebulizers, ultrasonic nebulizers, pulsating membrane nebulizers, nebulizers with a vibrating mesh or plate with multiple apertures, and nebulizers comprising a vibration generator and an aqueous chamber (e.g., Pari eFlow®).

Commercially available nebulizers suitable for use in the present invention can include the Aeroneb®, MicroAir®, Aeroneb® Pro, and Aeroneb® Go, Aeroneb® Solo, Aeroneb® Solo/Idehaler combination, Aeroneb® Solo or Go Idehaler-Pocket® combination, PARI LC-Plus®, PARI LC-Star®, PARI Sprint®, eFlow and eFlow Rapid®, Pari Boy® N and Pari Duraneb® (PARI, GmbH), MicroAir® (Omron Healthcare, Inc.), Halolite® (Profile Therapeutics Inc.), Respimat® (Boehringer Ingelheim), Aerodose® (Aerogen, Inc, Mountain View, CA), Omron Elite® (Omron Healthcare, Inc.), Omron Microair® (Omron Healthcare, Inc.), Mabismist II® (Mabis Healthcare, Inc.), Lumiscope® 6610, (The Lumiscope Company, Inc.), Airsep Mystique®, (AirSep Corporation), Acorn-1 and Acorn-II (Vital Signs, Inc.), Aquatower® (Medical Industries America), Ava-Neb® (Hudson Respiratory Care Incorporated), Cirrus® (Intersurgical Incorporated), Dart® (Professional Medical

02 May 2016
2012212269

Products), Devilbiss® Pulmo Aide (DeVilbiss Corp.), Downdraft® (Marquest), Fan Jet® (Marquest), MB-5 (Mefar), Misty Neb® (Baxter), Salter 8900 (Salter Labs), Sidestream® (Medic-Aid), Updraft-II® (Hudson Respiratory Care), Whisper Jet® (Marquest Medical Products), Aiolos® (Aiolos Medicnnsk Teknik), Inspiron® (Intertech Resources, Inc.),

5 Optimist® (Unomedical Inc.), Prodomo®, Spira® (Respiratory Care Center), AERx® and AERx Essence™ (Aradigm), Respingard II®, Sonik® LDI Nebulizer (Evit Labs), Swirler W Radioaerosol System (AMICI, Inc.), Maquet SUN 145 ultrasonic, Schill untrasonic, compare and compare Elite from Omron, Monoghan AeroEclipse BAN, Transneb, DeVilbiss 800, AerovectRx, Porta-Neb®, Freeway Freedom™, Sidestream, Ventstream and I-neb produced

10 by Philips, Inc.. By further non-limiting example, U.S. Patent No. 6,196,219, is hereby incorporated by reference in its entirety.

Any of these and other known nebulizers suitable to provide delivery of a aqueous inhalation medicament as described herein may be used in the various embodiments and methods described herein. In some embodiments, the nebulizers are available from, e.g., Pari

15 GmbH (Starnberg, Germany), DeVilbiss Healthcare (Heston, Middlesex, UK), Healthdyne, Vital Signs, Baxter, Allied Health Care, Invacare, Hudson, Omron, Bredem, AirSep, Luminscope, Medisana, Siemens, Aerogen, Mountain Medical, Aerosol Medical Ltd. (Colchester, Essex, UK), AFP Medical (Rugby, Warwickshire, UK), Bard Ltd. (Sunderland, UK), Carri-Med Ltd. (Dorking, UK), Plaem Nuiva (Brescia, Italy), Henleys Medical Supplies

20 (London, UK), Intersurgical (Berkshire, UK), Lifecare Hospital Supplies (Leies, UK), Medic-Aid Ltd. (West Sussex, UK), Medix Ltd. (Essex, UK), Sinclair Medical Ltd. (Surrey, UK), and many others.

Other nebulizers suitable for use in the methods and systems describe herein can include, but are not limited to, jet nebulizers (optionally sold with compressors), ultrasonic

25 nebulizers, and others. Exemplary jet nebulizers for use herein can include Pari LC plus/ProNeb, Pari LC plus/ProNeb Turbo, Pari LCPlus/Dura Neb 1000 & 2000 Pari LC plus/Walkhaler, Pari LC plus/Pari Master, Pari LC star, Omron CompAir XL Portable Nebulizer System (NE-C18 and JetAir Disposable nebulizer), Omron compare Elite Compressor Nebulizer System (NE-C21 and Elite Air Reusable Nebulizer, Pari LC Plus or

30 Pari LC Star nebulizer with Proneb Ultra compressor, Pulomo- aide, Pulmo-aide LT, Pulmo-aide traveler, Invacare Passport, Inspiration Healthdyne 626, Pulmo-Neb Traveler, DeVilbiss

02 May 2016
2012212269

646, Whisper Jet, AcornII, Misty-Neb, Allied aerosol, Schuco Home Care, Lexan Plasic Pocet Neb, SideStream Hand Held Neb, Mobil Mist, Up-Draft, Up-DraftII, T Up-Draft, ISO-NEB, Ava-Neb, Micro Mist, and PulmoMate.

Exemplary ultrasonic nebulizers suitable to provide delivery of a medicament as described herein can include MicroAir, UltraAir, Siemens Ultra Nebulizer 145, CompAir, Pulmosonic, Scout, 5003 Ultrasonic Neb, 5110 Ultrasonic Neb, 5004 Desk Ultrasonic Nebulizer, Mystique Ultrasonic, Lumiscope's Ultrasonic Nebulizer, Medisana Ultrasonic Nebulizer, Microstat Ultrasonic Nebulizer, and Mabismist Hand Held Ultrasonic Nebulizer. Other nebulizers for use herein include 5000 Electromagnetic Neb, 5001 Electromagnetic Neb 5002 Rotary Piston Neb, Lumineb I Piston Nebulizer 5500, Aeroneb Portable Nebulizer System, Aerodose Inhaler, and AeroEclipse Breath Actuated Nebulizer. Exemplary nebulizers comprising a vibrating mesh or plate with multiple apertures are described by R. Dhand in New Nebuliser Technology—Aerosol Generation by Using a Vibrating Mesh or Plate with Multiple Apertures, Long-Term Healthcare Strategies 2003, (July 2003), p. 1-4 and Respiratory Care, 47: 1406-1416 (2002), the entire disclosure of each of which is hereby incorporated by reference.

Additional nebulizers suitable for use in the presently described invention include nebulizers comprising a vibration generator and an aqueous chamber. Such nebulizers are sold commercially as, e.g., Pari eFlow, and are described in U.S. Patent Nos. 6,962,151, 5,518,179, 5,261,601, and 5,152,456, each of which is specifically incorporated by reference herein.

The parameters used in nebulization, such as flow rate, mesh membrane size, aerosol inhalation chamber size, mask size and materials, valves, and power source may be varied as applicable to provide delivery of a medicament as described herein to maximize their use with different types and aqueous inhalation mixtures.

In some embodiments, the drug solution is formed prior to use of the nebulizer by a patient. In other embodiments, the drug is stored in the nebulizer in liquid form, which may include a suspension, solution, or the like. In other embodiments, the drug is store in the nebulizer in solid form. In this case, the solution is mixed upon activation of the nebulizer, such as described in U.S. Patent No. 6,427,682 and PCT Publication No. WO 03/035030, both of which are hereby incorporated by reference in their entirety. In these nebulizers, the

02 May 2016
2012212269

solid drug, optionally combined with excipients to form a solid composition, is stored in a separate compartment from a liquid solvent.

The liquid solvent is capable of dissolving the solid composition to form a liquid composition, which can be aerosolized and inhaled. Such capability is, among other factors, a function of the selected amount and, potentially, the composition of the liquid. To allow easy handling and reproducible dosing, the sterile aqueous liquid may be able to dissolve the solid composition within a short period of time, possibly under gentle shaking. In some embodiments, the final liquid is ready to use after no longer than about 30 seconds. In some cases, the solid composition is dissolved within about 20 seconds, and advantageously, within about 10 seconds. As used herein, the terms “dissolve(d)”, “dissolving”, and “dissolution” refer to the disintegration of the solid composition and the release, *i.e.*, the dissolution, of the active compound. As a result of dissolving the solid composition with the liquid solvent a liquid composition is formed in which the active compound is contained in the dissolved state. As used herein, the active compound is in the dissolved state when at least about 90 wt.-% are dissolved, and more preferably when at least about 95 wt.-% are dissolved.

With regard to basic separated-compartment nebulizer design, it primarily depends on the specific application whether it is more useful to accommodate the aqueous liquid and the solid composition within separate chambers of the same container or primary package, or whether they should be provided in separate containers. If separate containers are used, these are provided as a set within the same secondary package. The use of separate containers is especially preferred for nebulizers containing two or more doses of the active compound. There is no limit to the total number of containers provided in a multi-dose kit. In one embodiment, the solid composition is provided as unit doses within multiple containers or within multiple chambers of a container, whereas the liquid solvent is provided within one chamber or container. In this case, a favorable design provides the liquid in a metered-dose dispenser, which may consist of a glass or plastic bottle closed with a dispensing device, such as a mechanical pump for metering the liquid. For instance, one actuation of the pumping mechanism may dispense the exact amount of liquid for dissolving one dose unit of the solid composition.

In another embodiment for multiple-dose separated-compartment nebulizers, both the solid composition and the liquid solvent are provided as matched unit doses within multiple

02 May 2016

2012212269

containers or within multiple chambers of a container. For instance, two-chambered containers can be used to hold one unit of the solid composition in one of the chambers and one unit of liquid in the other. As used herein, one unit is defined by the amount of drug present in the solid composition, which is one unit dose. Such two-chambered containers
5 may, however, also be used advantageously for nebulizers containing only one single drug dose.

In one embodiment of a separated-compartment nebulizer, a blister pack having two blisters is used, the blisters representing the chambers for containing the solid composition and the liquid solvent in matched quantities for preparing a dose unit of the final liquid
10 composition. As used herein, a blister pack represents a thermoformed or pressure-formed primary packaging unit, most likely comprising a polymeric packaging material that optionally includes a metal foil, such as aluminum. The blister pack may be shaped to allow easy dispensing of the contents. For instance, one side of the pack may be tapered or have a tapered portion or region through which the content is dispensable into another vessel upon
15 opening the blister pack at the tapered end. The tapered end may represent a tip.

In some embodiments, the two chambers of the blister pack are connected by a channel, the channel being adapted to direct fluid from the blister containing the liquid solvent to the blister containing the solid composition. During storage, the channel is closed with a seal. In this sense, a seal is any structure that prevents the liquid solvent from
20 contacting the solid composition. The seal is preferably breakable or removable; breaking or removing the seal when the nebulizer is to be used will allow the liquid solvent to enter the other chamber and dissolve the solid composition. The dissolution process may be improved by shaking the blister pack. Thus, the final liquid composition for inhalation is obtained, the liquid being present in one or both of the chambers of the pack connected by the channel,
25 depending on how the pack is held.

According to another embodiment, one of the chambers, preferably the one that is closer to the tapered portion of the blister pack communicates with a second channel, the channel extending from the chamber to a distal position of the tapered portion. During storage, this second channel does not communicate with the outside of the pack but is closed
30 in an air-tight fashion. Optionally, the distal end of the second channel is closed by a

02 May 2016
2012212269

breakable or removable cap or closure, which may *e.g.*, be a twist-off cap, a break-off cap, or a cut-off cap.

5 In one embodiment, a vial or container having two compartments is used, the compartment representing the chambers for containing the solid composition and the liquid solvent in matched quantities for preparing a dose unit of the final liquid composition. The liquid composition and a second liquid solvent may be contained in matched quantities for preparing a dose unit of the final liquid composition (by non-limiting example in cases where two soluble excipients or the pirfenidone or pyridone analog compound and excipient are unstable for storage, yet desired in the same mixture for administration.

10 In some embodiments, the two compartments are physically separated but in fluid communication such as when so the vial or container are connected by a channel or breakable barrier, the channel or breakable barrier being adapted to direct fluid between the two compartments to enable mixing prior to administration. During storage, the channel is closed with a seal or the breakable barrier intact. In this sense, a seal is any structure that prevents
15 mixing of contents in the two compartments. The seal is preferably breakable or removable; breaking or removing the seal when the nebulizer is to be used will allow the liquid solvent to enter the other chamber and dissolve the solid composition or in the case of two liquids permit mixing. The dissolution or mixing process may be improved by shaking the container. Thus, the final liquid composition for inhalation is obtained, the liquid being present in one or
20 both of the chambers of the pack connected by the channel or breakable barrier, depending on how the pack is held.

The solid composition itself can be provided in various different types of dosage forms, depending on the physicochemical properties of the drug, the desired dissolution rate, cost considerations, and other criteria. In one of the embodiments, the solid composition is a
25 single unit. This implies that one unit dose of the drug is comprised in a single, physically shaped solid form or article. In other words, the solid composition is coherent, which is in contrast to a multiple unit dosage form, in which the units are incoherent.

30 Examples of single units which may be used as dosage forms for the solid composition include tablets, such as compressed tablets, film-like units, foil-like units, wafers, lyophilized matrix units, and the like. In a preferred embodiment, the solid composition is a highly porous lyophilized form. Such lyophilizates, sometimes also called

02 May 2016
2012212269

wafers or lyophilized tablets, are particularly useful for their rapid disintegration, which also enables the rapid dissolution of the active compound.

On the other hand, for some applications the solid composition may also be formed as a multiple unit dosage form as defined above. Examples of multiple units are powders, granules, microparticles, pellets, beads, lyophilized powders, and the like. In one embodiment, the solid composition is a lyophilized powder. Such a dispersed lyophilized system comprises a multitude of powder particles, and due to the lyophilization process used in the formation of the powder, each particle has an irregular, porous microstructure through which the powder is capable of absorbing water very rapidly, resulting in quick dissolution.

Another type of multiparticulate system which is also capable of achieving rapid drug dissolution is that of powders, granules, or pellets from water-soluble excipients which are coated with the drug, so that the drug is located at the outer surface of the individual particles. In this type of system, the water-soluble low molecular weight excipient is useful for preparing the cores of such coated particles, which can be subsequently coated with a coating composition comprising the drug and, preferably, one or more additional excipients, such as a binder, a pore former, a saccharide, a sugar alcohol, a film-forming polymer, a plasticizer, or other excipients used in pharmaceutical coating compositions.

In another embodiment, the solid composition resembles a coating layer that is coated on multiple units made of insoluble material. Examples of insoluble units include beads made of glass, polymers, metals, and mineral salts. Again, the desired effect is primarily rapid disintegration of the coating layer and quick drug dissolution, which is achieved by providing the solid composition in a physical form that has a particularly high surface-to-volume ratio. Typically, the coating composition will, in addition to the drug and the water-soluble low molecular weight excipient, comprise one or more excipients, such as those mentioned above for coating soluble particles, or any other excipient known to be useful in pharmaceutical coating compositions.

To achieve the desired effects, it may be useful to incorporate more than one water-soluble low molecular weight excipient into the solid composition. For instance, one excipient may be selected for its drug carrier and diluent capability, while another excipient may be selected to adjust the pH. If the final liquid composition needs to be buffered, two excipients that together form a buffer system may be selected.

02 May 2016
2012212269

In one embodiment, the liquid to be used in a separated-compartment nebulizer is an aqueous liquid, which is herein defined as a liquid whose major component is water. The liquid does not necessarily consist of water only; however, in one embodiment it is purified water. In another embodiment, the liquid contains other components or substances, preferably other liquid components, but possibly also dissolved solids. Liquid components other than water which may be useful include propylene glycol, glycerol, and polyethylene glycol. One of the reasons to incorporate a solid compound as a solute is that such a compound is desirable in the final liquid composition, but is incompatible with the solid composition or with a component thereof, such as the active ingredient.

Another desirable characteristic for the liquid solvent is that it is sterile. An aqueous liquid would be subject to the risk of considerable microbiological contamination and growth if no measures were taken to ensure sterility. In order to provide a substantially sterile liquid, an effective amount of an acceptable antimicrobial agent or preservative can be incorporated or the liquid can be sterilized prior to providing it and to seal it with an air-tight seal. In one embodiment, the liquid is a sterilized liquid free of preservatives and provided in an appropriate air-tight container. However, according to another embodiment in which the nebulizer contains multiple doses of the active compound, the liquid may be supplied in a multiple-dose container, such as a metered-dose dispenser, and may require a preservative to prevent microbial contamination after the first use.

High Efficiency Liquid Nebulizers

High efficiency liquid nebulizers are inhalation devices that are adapted to deliver a large fraction of a loaded dose to a patient. Some high efficiency liquid nebulizers utilize microperforated membranes. In some embodiments, the high efficiency liquid nebulizer also utilizes one or more actively or passively vibrating microperforated membranes. In some embodiments, the high efficiency liquid nebulizer contains one or more oscillating membranes. In some embodiments, the high efficiency liquid nebulizer contains a vibrating mesh or plate with multiple apertures and optionally a vibration generator with an aerosol mixing chamber. In some such embodiments, the mixing chamber functions to collect (or stage) the aerosol from the aerosol generator. In some embodiments, an inhalation valve is also used to allow an inflow of ambient air into the mixing chamber during an inhalation phase and is closed to prevent escape of the aerosol from the mixing chamber during an

02 May 2016

2012212269

exhalation phase. In some such embodiments, the exhalation valve is arranged at a mouthpiece which is removably mounted at the mixing chamber and through which the patient inhales the aerosol from the mixing chamber. In yet some other embodiments, the high efficiency liquid nebulizer contains a pulsating membrane. In some embodiments, the high efficiency liquid nebulizer is continuously operating.

In some embodiments, the high efficiency liquid nebulizer contains a vibrating microperforated membrane of tapered nozzles against a bulk liquid will generate a plume of droplets without the need for compressed gas. In these embodiments, a solution in the microperforated membrane nebulizer is in contact with a membrane, the opposite side of which is open to the air. The membrane is perforated by a large number of nozzle orifices of an atomizing head. An aerosol is created when alternating acoustic pressure in the solution is built up in the vicinity of the membrane causing the fluid on the liquid side of the membrane to be emitted through the nozzles as uniformly sized droplets.

Some embodiments the high efficiency liquid nebulizers use passive nozzle membranes and a separate piezoelectric transducer that are in contact with the solution. In contrast, some high efficiency liquid nebulizers employ an active nozzle membrane, which use the acoustic pressure in the nebulizer to generate very fine droplets of solution via the high frequency vibration of the nozzle membrane.

Some high efficiency liquid nebulizers contain a resonant system. In some such high efficiency liquid nebulizers, the membrane is driven by a frequency for which the amplitude of the vibrational movement at the center of the membrane is particularly large, resulting in a focused acoustic pressure in the vicinity of the nozzle; the resonant frequency may be about 100kHz. A flexible mounting is used to keep unwanted loss of vibrational energy to the mechanical surroundings of the atomizing head to a minimum. In some embodiments, the vibrating membrane of the high efficiency liquid nebulizer may be made of a nickel-palladium alloy by electroforming.

In some embodiments, the high efficiency liquid nebulizer (i) achieves lung deposition of at least about 5%, at least about 6%, at least about 7%, at least about 8%, at least about 9%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least

02 May 2016
2012212269

about 75%, at least about 80%, or at least about 85%, based on the nominal dose of the pirfenidone or pyridone analog compound administered to the mammal.

In some embodiments, the high efficiency liquid nebulizer (ii) provides a Geometric Standard Deviation (GSD) of emitted droplet size distribution of the solution administered with the high efficiency liquid nebulizer of about 1.0 μm to about 2.5 μm , about 1.2 μm to about 2.5 μm , about 1.3 μm to about 2.0 μm , at least about 1.4 μm to about 1.9 μm , at least about 1.5 μm to about 1.9 μm , about 1.5 μm , about 1.7 μm , or about 1.9 μm .

In some embodiments, the high efficiency liquid nebulizer (iii) provides a mass median aerodynamic diameter (MMAD) of droplet size of the solution emitted with the high efficiency liquid nebulizer of about 1 μm to about 5 μm , about 2 to about 4 μm , or about 2.5 to about 4.0 μm . In some embodiments, the high efficiency liquid nebulizer (iii) provides a volumetric mean diameter (VMD) 1 μm to about 5 μm , about 2 to about 4 μm , or about 2.5 to about 4.0 μm . In some embodiments, the high efficiency liquid nebulizer (iii) provides a mass median diameter (MMD) 1 μm to about 5 μm , about 2 to about 4 μm , or about 2.5 to about 4.0 μm .

In some embodiments, the high efficiency liquid nebulizer (iv) provides a fine particle fraction (FPF= % \leq 5 microns) of droplets emitted from the high efficiency nebulizer of at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, or at least about 90%.

In some embodiments, the high efficiency liquid nebulizer (v) provides an output rate of at least 0.1 mL/min, at least 0.2 mL/min, at least 0.3 mL/min, at least 0.4 mL/min, at least 0.5 mL/min, at least 0.6 mL/min, at least 0.8 mL/min, or at least 1.0 mL/min.

In some embodiments, the high efficiency liquid nebulizer (vi) delivers at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, or at least about 80% of the fill volume to the mammal.

In some embodiments, the high efficiency liquid nebulizer provides an RDD of at least about 5%, at least about 6%, at least about 7%, at least about 8%, at least about 9%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least

02 May 2016
2012212269

about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, or at least about 85%.

In some embodiments, the high efficiency liquid nebulizer is characterized as providing one or more of (i), (ii), (iii) (iv), (v), or (vi). In some embodiments, the high efficiency liquid nebulizer is characterized as providing at least one, at least two, at least three, at least four, at least five, or all six of (i), (ii), (iii) (iv), (v), or (vi).

Additional features of a high efficiency liquid nebulizer with perforated membranes are disclosed in U.S. Pat. Nos. 6,962,151, 5,152,456, 5,261,601, and 5,518,179, US 6,983,747, each of which is hereby incorporated by reference in its entirety. Other embodiments of the high efficiency liquid nebulizers contain oscillatable membranes. Features of these high efficiency liquid nebulizers are disclosed in 7,252,085; 7,059, 320; 6,983,747, each of which is hereby incorporated by reference in its entirety.

Commercial high efficiency liquid nebulizers are available from: PARI (Germany) under the trade name eFlow®; Nektar Therapeutics (San Carlos, CA) under the trade names AeroNeb® Go and AeroNeb® Pro, and AeroNeb® Solo, Respironics (Murrysville, CA) under the trade names I-Neb®, Omron (Bannockburn, IL) under the trade name Micro-Air®, and Activaero (Germany) under the trade name Akita®. Commercial High Efficiency Nebulizers are also available from Aerogen (Galaway, Ireland) utilizing the OnQ® nebulizer technology.

Meter Dose Inhaler (MDI)

A propellant driven inhaler (pMDI) releases a metered dose of medicine upon each actuation. The medicine is formulated as a suspension or solution of a drug substance in a suitable propellant such as a halogenated hydrocarbon. pMDIs are described in, for example, Newman, S. P., Aerosols and the Lung, Clarke et al., eds., pp. 197-224 (Butterworths, London, England, 1984).

In some embodiments, the particle size of the drug substance in an MDI may be optimally chosen. In some embodiments, the particles of active ingredient have diameters of less than about 50 microns. In some embodiments, the particles have diameters of less than about 10 microns. In some embodiments, the particles have diameters of from about 1 micron to about 5 microns. In some embodiments, the particles have diameters of less than about 1 micron. In one advantageous embodiment, the particles have diameters of from about 2 microns to about 5 microns.

02 May 2016
2012212269

By non-limiting example, metered-dose inhalers (MDI), the pirfenidone or pyridone analog compound disclosed herein are prepared in dosages to deliver from about 34 mcg to about 463 mg from a formulation meeting the requirements of the MDI. The pirfenidone or pyridone analog compound disclosed herein may be soluble in the propellant, soluble in the propellant plus a co-solvent (by non-limiting example ethanol), soluble in the propellant plus an additional moiety promoting increased solubility (by non-limiting example glycerol or phospholipid), or as a stable suspension or micronized, spray-dried or nanosuspension.

By non-limiting example, a metered-dose pirfenidone or pyridone analog compound may be administered in the described respirable delivered dose in 10 or fewer inhalation breaths, more preferably in 8 or fewer inhalation breaths, more preferably in 6 or fewer inhalation breaths, more preferably in 4 or fewer inhalation breaths, more preferably in 2 or fewer inhalation breaths.

The propellants for use with the MDIs may be any propellants known in the art. Examples of propellants include chlorofluorocarbons (CFCs) such as

dichlorodifluoromethane, trichlorofluoromethane, and dichlorotetrafluoroethane; hydrofluoroalkanes (HFAs); and carbon dioxide. It may be advantageous to use HFAs instead of CFCs due to the environmental concerns associated with the use of CFCs.

Examples of medicinal aerosol preparations containing HFAs are presented in U.S. Patent Nos. 6,585,958; 2,868,691 and 3,014,844, all of which are hereby incorporated by reference in their entirety. In some embodiments, a co-solvent is mixed with the propellant to facilitate dissolution or suspension of the drug substance.

In some embodiments, the propellant and active ingredient are contained in separate containers, such as described in U.S. Patent No. 4,534,345, which is hereby incorporated by reference in its entirety.

In some embodiments, the MDI used herein is activated by a patient pushing a lever, button, or other actuator. In other embodiments, the release of the aerosol is breath activated such that, after initially arming the unit, the active compound aerosol is released once the patient begins to inhale, such as described in U.S. Patent Nos. 6,672,304; 5,404,871; 5,347,998; 5,284,133; 5,217,004; 5,119,806; 5,060,643; 4,664,107; 4,648,393; 3,789,843; 3,732,864; 3,636,949; 3,598,294; 3,565,070; 3,456,646; 3,456,645; and 3,456,644, each of which is hereby incorporated by reference in its entirety. Such a system enables more of the

active compound to get into the lungs of the patient. Another mechanism to help a patient get adequate dosage with the active ingredient may include a valve mechanism that allows a patient to use more than one breath to inhale the drug, such as described in U.S. Patent Nos. 4,470,412 and 5,385,140, both of which are hereby incorporated by reference in their entirety.

Additional examples of MDIs known in the art and suitable for use herein include U.S. Patent Nos. 6,435,177; 6,585,958; 5,642,730; 6,223,746; 4,955,371; 5,404,871; 5,364,838; and 6,523,536, all of which are hereby incorporated by reference in their entirety.

Dry Powder Inhaler (DPI)

There are two major designs of dry powder inhalers. One design is the metering device in which a reservoir for the drug is placed within the device and the patient adds a dose of the drug into the inhalation chamber. The second is a factory-metered device in which each individual dose has been manufactured in a separate container. Both systems depend upon the formulation of drug into small particles of mass median diameters from about 1 to about 5 micron, and usually involve co-formulation with larger excipient particles (typically 100 micron diameter lactose particles). Drug powder is placed into the inhalation chamber (either by device metering or by breakage of a factory-metered dosage) and the inspiratory flow of the patient accelerates the powder out of the device and into the oral cavity. Non-laminar flow characteristics of the powder path cause the excipient-drug aggregates to decompose, and the mass of the large excipient particles causes their impaction at the back of the throat, while the smaller drug particles are deposited deep in the lungs.

As with liquid nebulization and MDIs, particle size of the pirfenidone or pyridone analog compound aerosol formulation may be optimized. If the particle size is larger than about 5 micron MMAD then the particles are deposited in upper airways. If the particle size of the aerosol is smaller than about 1 micron then it is delivered into the alveoli and may get transferred into the systemic blood circulation.

By non-limiting example, in dry powder inhalers, the pirfenidone or pyridone analog compound disclosed herein are prepared in dosages to disperse and deliver from about 34 mcg to about 463 mg from a dry powder formulation.

By non-limiting example, a dry powder pirfenidone or pyridone analog compound may be administered in the described respirable delivered dose in 10 or fewer inhalation

02 May 2016
2012212269

breaths, more preferably in 8 or fewer inhalation breaths, more preferably in 6 or fewer inhalation breaths, more preferably in 8 or fewer inhalation breaths, more preferably in 4 or fewer inhalation breaths, more preferably in 2 or fewer inhalation breaths.

In some embodiments, a dry powder inhaler (DPI) is used to dispense the pirfenidone or pyridone analog compound described herein. DPIs contain the drug substance in fine dry particle form. Typically, inhalation by a patient causes the dry particles to form an aerosol cloud that is drawn into the patient's lungs. The fine dry drug particles may be produced by any technique known in the art. Some well-known techniques include use of a jet mill or other comminution equipment, precipitation from saturated or super saturated solutions, spray drying, in situ micronization (Hovione), or supercritical fluid methods. Typical powder formulations include production of spherical pellets or adhesive mixtures. In adhesive mixtures, the drug particles are attached to larger carrier particles, such as lactose monohydrate of size about 50 to about 100 microns in diameter. The larger carrier particles increase the aerodynamic forces on the carrier/drug agglomerates to improve aerosol formation. Turbulence and/or mechanical devices break the agglomerates into their constituent parts. The smaller drug particles are then drawn into the lungs while the larger carrier particles deposit in the mouth or throat. Some examples of adhesive mixtures are described in U.S. Patent No. 5,478,578 and PCT Publication Nos. WO 95/11666, WO 87/05213, WO 96/23485, and WO 97/03649, all of which are incorporated by reference in their entirety. Additional excipients may also be included with the drug substance.

There are three common types of DPIs, all of which may be used with the pirfenidone or pyridone analog compounds described herein. In a single-dose DPI, a capsule containing one dose of dry drug substance/excipients is loaded into the inhaler. Upon activation, the capsule is breached, allowing the dry powder to be dispersed and inhaled using a dry powder inhaler. To dispense additional doses, the old capsule must be removed and an additional capsule loaded. Examples of single-dose DPIs are described in U.S. Patent Nos. 3,807,400; 3,906,950; 3,991,761; and 4,013,075, all of which are hereby incorporated by reference in their entirety. In a multiple unit dose DPI, a package containing multiple single dose compartments is provided. For example, the package may comprise a blister pack, where each blister compartment contains one dose. Each dose can be dispensed upon breach of a blister compartment. Any of several arrangements of compartments in the package can be

02 May 2016
2012212269

used. For example, rotary or strip arrangements are common. Examples of multiple unit does DPIs are described in EPO Patent Application Publication Nos. 0211595A2, 0455463A1, and 0467172A1, all of which are hereby incorporated by reference in their entirety. In a multi-dose DPI, a single reservoir of dry powder is used. Mechanisms are provided that measure out single dose amounts from the reservoir to be aerosolized and inhaled, such as described in U.S. Patent Nos. 5,829,434; 5,437,270; 2,587,215; 5,113,855; 5,840,279; 4,688,218; 4,667,668; 5,033,463; and 4,805,811 and PCT Publication No. WO 92/09322, all of which are hereby incorporated by reference in their entirety.

In some embodiments, auxiliary energy in addition to or other than a patient's inhalation may be provided to facilitate operation of a DPI. For example, pressurized air may be provided to aid in powder de-agglomeration, such as described in U.S. Patent Nos. 3,906,950; 5,113,855; 5,388,572; 6,029,662 and PCT Publication Nos. WO 93/12831, WO 90/07351, and WO 99/62495, all of which are hereby incorporated by reference in their entirety. Electrically driven impellers may also be provided, such as described in U.S. Patent Nos. 3,948,264; 3,971,377; 4,147,166; 6,006,747 and PCT Publication No. WO 98/03217, all of which are hereby incorporated by reference in their entirety. Another mechanism is an electrically powered tapping piston, such as described in PCT Publication No. WO 90/13327, which is hereby incorporated by reference in its entirety. Other DPIs use a vibrator, such as described in U.S. Patent Nos. 5,694,920 and 6,026,809, both of which are hereby incorporated by reference in their entirety. Finally, a scraper system may be employed, such as described in PCT Publication No. WO 93/24165, which is hereby incorporated by reference in its entirety.

Additional examples of DPIs for use herein are described in U.S. Patent Nos. 4,811,731; 5,113,855; 5,840,279; 3,507,277; 3,669,113; 3,635,219; 3,991,761; 4,353,365; 4,889,144; 4,907,538; 5,829,434; 6,681,768; 6,561,186; 5,918,594; 6,003,512; 5,775,320; 5,740,794; and 6,626,173, all of which are hereby incorporated by reference in their entirety.

In some embodiments, a spacer or chamber may be used with any of the inhalers described herein to increase the amount of drug substance that gets absorbed by the patient, such as is described in U.S. Patent Nos. 4,470,412; 4,790,305; 4,926,852; 5,012,803; 5,040,527; 5,024,467; 5,816,240; 5,027,806; and 6,026,807, all of which are hereby incorporated by reference in their entirety. For example, a spacer may delay the time from

02 May 2016

2012212269

aerosol production to the time when the aerosol enters a patient's mouth. Such a delay may improve synchronization between the patient's inhalation and the aerosol production. A mask may also be incorporated for infants or other patients that have difficulty using the traditional mouthpiece, such as is described in U.S. Patent Nos. 4,809,692; 4,832,015; 5,012,804; 5,427,089; 5,645,049; and 5,988,160, all of which are hereby incorporated by reference in their entirety.

Dry powder inhalers (DPIs), which involve deaggregation and aerosolization of dry powder particles, normally rely upon a burst of inspired air that is drawn through the unit to deliver a drug dosage. Such devices are described in, for example, U.S. Pat. No. 4,807,814, which is directed to a pneumatic powder ejector having a suction stage and an injection stage; SU 628930 (Abstract), describing a hand-held powder disperser having an axial air flow tube; Fox et al., Powder and Bulk Engineering, pages 33-36 (March 1988), describing a venturi eductor having an axial air inlet tube upstream of a venturi restriction; EP 347 779, describing a hand-held powder disperser having a collapsible expansion chamber, and U.S. Pat. No. 5,785,049, directed to dry powder delivery devices for drugs.

Commercial examples of dry powder inhalers that can be used with the pirfenidone or pyridone analog compound formulations described herein include the Aerolizer, Turohaler, Handihaler and Discus.

Solution/Dispersion Formulations

In one embodiment, aqueous formulations containing soluble or nanoparticulate drug particles are provided. For aqueous aerosol formulations, the drug may be present at a concentration from about 34 mcg/mL to about 463 mg/mL. In some embodiments the drug is present at a concentration from about 1 mg/mL to about 463 mg/mL, or about 1 mg/mL to about 400 mg/mL, or about 0.1 mg/mL to about 360 mg/mL, or about 1 mg/mL to about 300 mg/mL, or about 1 mg/mL to about 200 mg/mL, about 1 mg/mL to about 100 mg/mL, or about 1 mg/mL to about 50 mg/mL, or about 5 mg/mL to about 50 mg/mL, or about 10 mg/mL to about 50 mg/mL, or about 15 mg/mL to about 50 mg/mL, or about 20 mg/mL to about 50 mg/mL. Such formulations provide effective delivery to appropriate areas of the lung, with the more concentrated aerosol formulations having the additional advantage of enabling large quantities of drug substance to be delivered to the lung in a very short period of time. In one embodiment, a formulation is optimized to provide a well tolerated

02 May 2016
2012212269

formulation. Accordingly, in one embodiment, pirfenidone or pyridone analog compound disclosed herein are formulated to have good taste, pH from about 4.0 to about 8.0, osmolarity from about 100 to about 5000 mOsmol/kg. In some embodiments, the osmolarity is from about 100 to about 1000 mOsmol/kg. In some embodiments, the osmolarity is from about 200 to about 500 mOsmol/kg. In some embodiments, the permeant ion concentration is from about 30 to about 300 mM.

In some embodiments, described herein is an aqueous pharmaceutical composition comprising pirfenidone or pyridone analog compound, water and one or more additional ingredients selected from co-solvents, tonicity agents, sweeteners, surfactants, wetting agents, chelating agents, anti-oxidants, salts, and buffers. It should be understood that many excipients may serve several functions, even within the same formulation.

In some embodiments, pharmaceutical compositions described herein do not include any thickening agents.

In some embodiments, the concentration of pirfenidone or pyridone analog compound in the aqueous pharmaceutical composition is between about 0.1 mg/mL and about 100 mg/mL. In some embodiments, the concentration of pirfenidone or pyridone analog compound in the pharmaceutical composition is between about 1 mg/mL and about 100 mg/mL, between about 10 mg/mL and about 100 mg/mL between about 20 mg/mL and about 100 mg/mL, between about 25 mg/mL and about 100 mg/mL, between about 30 mg/mL and about 100 mg/mL, between about 15 mg/mL and about 50 mg/mL, between about 20 mg/mL and about 50 mg/mL, between about 25 mg/mL and about 50 mg/mL, or between about 30 mg/mL and about 50 mg/mL.

In some embodiments, the pH is between about pH 4.0 and about pH 8.0. In some embodiments, the pH is between about pH 5.0 and about pH 8.0. In some embodiments, the pH is between about pH 6.0 and about pH 8.0. In some embodiments, the pH is between about pH 6.5 and about pH 8.0.

In some embodiments, the aqueous pharmaceutical composition includes one or more co-solvents. In some embodiments, the aqueous pharmaceutical composition includes one or more co-solvents, where the total amount of co-solvents is from about 1% to about 50% v/v of the total volume of the composition. In some embodiments, the aqueous pharmaceutical composition includes one or more co-solvents, where the total amount of co-solvents is from

02 May 2016
2012212269

about 1% to about 50% v/v, from about 1% to about 40% v/v, from about 1% to about 30% v/v, or from about 1% to about 25% v/v, of the total volume of the composition. Co-solvents include, but are not limited to, ethanol, propylene glycol and glycerol. In some embodiments, the aqueous pharmaceutical composition includes ethanol at about 1% v/v to about 25%. In

5 some embodiments, the aqueous pharmaceutical composition includes ethanol at about 1% v/v to about 15%. In some embodiments, the aqueous pharmaceutical composition includes ethanol at about 1% v/v, 2% v/v, 3% v/v, 4% v/v, 5% v/v, 6% v/v, 7% v/v, 8% v/v, 9% v/v, 10% v/v, 11% v/v, 12% v/v, 13% v/v, 14% v/v, 15% v/v, 16% v/v, 17% v/v, 18% v/v, 19% v/v, 20% v/v, 21% v/v, 22% v/v, 23% v/v, 24% v/v, or 25% v/v. In some embodiments, the

10 aqueous pharmaceutical composition includes glycerol at about 1% v/v to about 25%. In some embodiments, the aqueous pharmaceutical composition includes glycerol at about 1% v/v to about 15%. In some embodiments, the aqueous pharmaceutical composition includes glycerol at about 1% v/v, 2% v/v, 3% v/v, 4% v/v, 5% v/v, 6% v/v, 7% v/v, 8% v/v, 9% v/v, 10% v/v, 11% v/v, 12% v/v, 13% v/v, 14% v/v, 15% v/v, 16% v/v, 17% v/v, 18% v/v, 19%

15 v/v, 20% v/v, 21% v/v, 22% v/v, 23% v/v, 24% v/v, or 25% v/v. In some embodiments, the aqueous pharmaceutical composition includes propylene glycol at about 1% v/v to about 50%. In some embodiments, the aqueous pharmaceutical composition includes propylene glycol at about 1% v/v to about 25%. In some embodiments, the aqueous pharmaceutical composition includes propylene glycol at about 1% v/v, 2% v/v, 3% v/v, 4% v/v, 5% v/v, 6%

20 v/v, 7% v/v, 8% v/v, 9% v/v, 10% v/v, 11% v/v, 12% v/v, 13% v/v, 14% v/v, 15% v/v, 16% v/v, 17% v/v, 18% v/v, 19% v/v, 20% v/v, 21% v/v, 22% v/v, 23% v/v, 24% v/v, or 25% v/v.

In some embodiments, the aqueous pharmaceutical composition includes ethanol at about 1% v/v to about 25% and propylene glycol at about 1% v/v to about 50%. In some

embodiments, the aqueous pharmaceutical composition includes ethanol at about 1% v/v to about 15% and propylene glycol at about 1% v/v to about 30%. In some embodiments, the

25 aqueous pharmaceutical composition includes ethanol at about 1% v/v to about 8% and propylene glycol at about 1% v/v to about 16%. In some embodiments, the aqueous pharmaceutical composition includes ethanol and twice as much propylene glycol, based on volume.

02 May 2016
2012212269

In some embodiments, the aqueous pharmaceutical composition includes a buffer. In some embodiments, the buffer is a citrate buffer or a phosphate buffer. In some embodiments, the buffer is a citrate buffer. In some embodiments, the buffer is a phosphate buffer.

5 In some embodiments, the aqueous pharmaceutical composition consists essentially of pirfenidone or pyridone analog compound, water, ethanol and/or propylene glycol, a buffer to maintain the pH at about 4 to 8 and optionally one or more ingredients selected from salts, surfactants, and sweeteners (taste-masking agents). In some embodiments, the one or more salts are selected from tonicity agents. In some embodiments, the one or more salts are selected from sodium chloride and magnesium chloride.

10 In some embodiments, the aqueous pharmaceutical composition consists essentially of pirfenidone or pyridone analog compound at a concentration of about 10 mg/mL to about 50mg/mL, water, one or two cosolvents (ethanol at a concentration of about 1% v/v to about 25% v/v and/or propylene glycol at a concentration of about 1% v/v to about 50% v/v), a buffer to maintain the pH at about 4 to 8 and optionally one or more ingredients selected from
15 salts, surfactants, and sweeteners (taste-masking agents).

In one embodiment, the solution or diluent used for preparation of aerosol formulations has a pH range from about 4.0 to about 8.0. This pH range improves tolerability. When the aerosol is either acidic or basic, it can cause bronchospasm and cough. Although the safe range of pH is relative and some patients may tolerate a mildly acidic
20 aerosol, while others will experience bronchospasm. Any aerosol with a pH of less than about 4.0 typically induces bronchospasm. Aerosols having pH greater than about 8.0 may have low tolerability because body tissues are generally unable to buffer alkaline aerosols. Aerosols with controlled pH below about 4.0 and over about 8.0 typically result in lung irritation accompanied by severe bronchospasm cough and inflammatory reactions. For these
25 reasons as well as for the avoidance of bronchospasm, cough or inflammation in patients, the optimum pH for the aerosol formulation was determined to be between about pH 4.0 to about pH 8.0.

By non-limiting example, compositions may also include a buffer or a pH adjusting agent, typically a salt prepared from an organic acid or base. Representative buffers include
30 organic acid salts of citric acid, ascorbic acid, gluconic acid, carbonic acid, tartaric acid,

02 May 2016

2012212269

succinic acid, acetic acid, or phthalic acid, Tris, tromethamine, hydrochloride, or phosphate buffers.

Many patients have increased sensitivity to various chemical tastes, including bitter, salt, sweet, metallic sensations. To create well-tolerated drug products, by non-limiting example taste masking may be accomplished through the addition of taste-masking excipients, adjusted osmolality, and sweeteners.

Many patients have increased sensitivity to various chemical agents and have high incidence of bronchospastic, asthmatic or other coughing incidents. Their airways are particularly sensitive to hypotonic or hypertonic and acidic or alkaline conditions and to the presence of any permanent ion, such as chloride. Any imbalance in these conditions or a presence of chloride above certain value leads to bronchospastic or inflammatory events and/or cough which greatly impair treatment with inhalable formulations. Both these conditions prevent efficient delivery of aerosolized drugs into the endobronchial space.

In some embodiments, the osmolality of aqueous solutions of the pirfenidone or pyridone analog compound disclosed herein are adjusted by providing excipients. In some cases, a certain amount of chloride or another anion is needed for successful and efficacious delivery of aerosolized pirfenidone or pyridone analog compound.

In some embodiments, the osmolality of aqueous solutions of the pirfenidone or pyridone analog compound disclosed herein is greater than 100 mOsmol/kg. In some embodiments, the osmolality of aqueous solutions of the pirfenidone or pyridone analog compound disclosed herein is greater than 300 mOsmol/kg. In some embodiments, the osmolality of aqueous solutions of the pirfenidone or pyridone analog compound disclosed herein is greater than 1000 mOsmol/kg. In some embodiments, aerosol delivery of aqueous solutions with high osmolality (i.e. greater than about 300 mOsmol/kg) have high incidence of bronchospastic, asthmatic or other coughing incidents. In some embodiments, aerosol delivery of the aqueous solutions having high osmolality (i.e. greater than about 300 mOsmol/kg) as described do not increase the incidence of bronchospastic, asthmatic or other coughing incidents.

In some embodiments, the osmolality of aqueous solutions of the pirfenidone or pyridone analog compound disclosed herein are greater than 100 mOsmol/kg above by providing excipients. In some cases, a certain amount of chloride or another anion is needed

02 May 2016
2012212269

for successful and efficacious delivery of aerosolized pirfenidone or pyridone analog compound

In some embodiments, the formulation for an aerosol pirfenidone or pyridone analog compound may comprise from about 34 mcg to about 463 mg pirfenidone or pyridone analog compound per about 1 to about 5 ml of dilute saline (between 1/10 to 2/1 normal saline).

Accordingly, the concentration of a pirfenidone or pyridone analog compound solution may be greater than about 34 mcg/ml, greater than about 463 mcg/ml, greater than about 1 mg/ml, greater than about 2 mg/mL, greater than about 3.0 mg/mL, greater than about 3.7 mg/mL, greater than about 10 mg/mL, greater than about 37 mg/mL, greater than about 50 mg/ml, greater than about 100 mg/mL, or greater than 463 mg/mL.

In some embodiments, solution osmolality is from about 100 mOsmol/kg to about 6000 mOsmol/kg. In some embodiments, solution osmolality is from about 100 mOsmol/kg to about 5000 mOsmol/kg. In some other embodiments, the solution osmolality is from about 400 mOsmol/kg to about 5000 mOsmol/kg.

In one embodiment, permeant ion concentration is from about 25 mM to about 400 mM. In various other embodiments, permeant ion concentration is from about 30 mM to about 300 mM; from about 40 mM to about 200 mM; and from about 50 mM to about 150 mM.

Solid Particle Formulations

In some embodiments, solid drug nanoparticles are provided for use in generating dry aerosols or for generating nanoparticles in liquid suspension. Powders comprising nanoparticulate drug can be made by spray-drying aqueous dispersions of a nanoparticulate drug and a surface modifier to form a dry powder which consists of aggregated drug nanoparticles. In one embodiment, the aggregates can have a size of about 1 to about 2 microns which is suitable for deep lung delivery. The aggregate particle size can be increased to target alternative delivery sites, such as the upper bronchial region or nasal mucosa by increasing the concentration of drug in the spray-dried dispersion or by increasing the droplet size generated by the spray dryer.

Alternatively, an aqueous dispersion of drug and surface modifier can contain a dissolved diluent such as lactose or mannitol which, when spray dried, forms respirable diluent particles, each of which contains at least one embedded drug nanoparticle and surface

02 May 2016
2012212269

modifier. The diluent particles with embedded drug can have a particle size of about 1 to about 2 microns, suitable for deep lung delivery. In addition, the diluent particle size can be increased to target alternate delivery sites, such as the upper bronchial region or nasal mucosa by increasing the concentration of dissolved diluent in the aqueous dispersion prior to spray drying, or by increasing the droplet size generated by the spray dryer.

Spray-dried powders can be used in DPIs or pMDIs, either alone or combined with freeze-dried nanoparticulate powder. In addition, spray-dried powders containing drug nanoparticles can be reconstituted and used in either jet or ultrasonic nebulizers to generate aqueous dispersions having respirable droplet sizes, where each droplet contains at least one drug nanoparticle. Concentrated nanoparticulate dispersions may also be used in these embodiments of the invention.

Nanoparticulate drug dispersions can also be freeze-dried to obtain powders suitable for nasal or pulmonary delivery. Such powders may contain aggregated nanoparticulate drug particles having a surface modifier. Such aggregates may have sizes within a respirable range, *e.g.*, about 1 to about 5 microns MMAD.

Freeze dried powders of the appropriate particle size can also be obtained by freeze drying aqueous dispersions of drug and surface modifier, which additionally contain a dissolved diluent such as lactose or mannitol. In these instances the freeze dried powders consist of respirable particles of diluent, each of which contains at least one embedded drug nanoparticle.

Freeze-dried powders can be used in DPIs or pMDIs, either alone or combined with spray-dried nanoparticulate powder. In addition, freeze-dried powders containing drug nanoparticles can be reconstituted and used in either jet or ultrasonic nebulizers to generate aqueous dispersions that have respirable droplet sizes, where each droplet contains at least one drug nanoparticle.

One embodiment of the invention is directed to a process and composition for propellant-based systems comprising nanoparticulate drug particles and a surface modifier. Such formulations may be prepared by wet milling the coarse drug substance and surface modifier in liquid propellant, either at ambient pressure or under high pressure conditions.

Alternatively, dry powders containing drug nanoparticles may be prepared by spray-drying or freeze-drying aqueous dispersions of drug nanoparticles and the resultant powders dispersed

02 May 2016

2012212269

into suitable propellants for use in conventional pMDIs. Such nanoparticulate pMDI formulations can be used for either nasal or pulmonary delivery. For pulmonary administration, such formulations afford increased delivery to the deep lung regions because of the small (*e.g.*, about 1 to about 2 microns MMAD) particle sizes available from these methods. Concentrated aerosol formulations can also be employed in pMDIs.

Another embodiment is directed to dry powders which contain nanoparticulate compositions for pulmonary or nasal delivery. The powders may consist of respirable aggregates of nanoparticulate drug particles, or of respirable particles of a diluent which contains at least one embedded drug nanoparticle. Powders containing nanoparticulate drug particles can be prepared from aqueous dispersions of nanoparticles by removing the water via spray-drying or lyophilization (freeze drying). Spray-drying is less time consuming and less expensive than freeze-drying, and therefore more cost-effective. However, certain drugs, such as biologicals benefit from lyophilization rather than spray-drying in making dry powder formulations.

Conventional micronized drug particles used in dry powder aerosol delivery having particle diameters of from about 1 to about 5 microns MMAD are often difficult to meter and disperse in small quantities because of the electrostatic cohesive forces inherent in such powders. These difficulties can lead to loss of drug substance to the delivery device as well as incomplete powder dispersion and sub-optimal delivery to the lung. Many drug compounds, particularly proteins and peptides, are intended for deep lung delivery and systemic absorption. Since the average particle sizes of conventionally prepared dry powders are usually in the range of from about 1 to about 5 microns MMAD, the fraction of material which actually reaches the alveolar region may be quite small. Thus, delivery of micronized dry powders to the lung, especially the alveolar region, is generally very inefficient because of the properties of the powders themselves.

The dry powder aerosols which contain nanoparticulate drugs can be made smaller than comparable micronized drug substance and, therefore, are appropriate for efficient delivery to the deep lung. Moreover, aggregates of nanoparticulate drugs are spherical in geometry and have good flow properties, thereby aiding in dose metering and deposition of the administered composition in the lung or nasal cavities.

02 May 2016
2012212269

Dry nanoparticulate compositions can be used in both DPIs and pMDIs. As used herein, "dry" refers to a composition having less than about 5% water.

In one embodiment, compositions are provided containing nanoparticles which have an effective average particle size of less than about 1000 nm, more preferably less than about 400 nm, less than about 300 nm, less than about 250 nm, or less than about 200 nm, as measured by light-scattering methods. By "an effective average particle size of less than about 1000 nm" it is meant that at least 50% of the drug particles have a weight average particle size of less than about 1000 nm when measured by light scattering techniques. Preferably, at least 70% of the drug particles have an average particle size of less than about 1000 nm, more preferably at least 90% of the drug particles have an average particle size of less than about 1000 nm, and even more preferably at least about 95% of the particles have a weight average particle size of less than about 1000 nm.

For aqueous aerosol formulations, the nanoparticulate pirfenidone or pyridone analog compound agent may be present at a concentration of about 34 mcg/mL up to about 463 mg/mL. For dry powder aerosol formulations, the nanoparticulate agent may be present at a concentration of about 34 mg/g up to about 463 mg/g, depending on the desired drug dosage. Concentrated nanoparticulate aerosols, defined as containing a nanoparticulate drug at a concentration of about 34 mcg/mL up to about 463 mg/mL for aqueous aerosol formulations, and about 34 mg/g up to about 463 mg/g for dry powder aerosol formulations, are specifically provided. Such formulations provide effective delivery to appropriate areas of the lung or nasal cavities in short administration times, *i.e.*, less than about 3-15 seconds per dose as compared to administration times of up to 4 to 20 minutes as found in conventional pulmonary nebulizer therapies.

Nanoparticulate drug compositions for aerosol administration can be made by, for example, (1) nebulizing a dispersion of a nanoparticulate drug, obtained by either grinding or precipitation; (2) aerosolizing a dry powder of aggregates of nanoparticulate drug and surface modifier (the aerosolized composition may additionally contain a diluent); or (3) aerosolizing a suspension of nanoparticulate drug or drug aggregates in a non-aqueous propellant. The aggregates of nanoparticulate drug and surface modifier, which may additionally contain a diluent, can be made in a non-pressurized or a pressurized non-aqueous system. Concentrated aerosol formulations may also be made via such methods.

02 May 2016
2012212269

Milling of aqueous drug to obtain nanoparticulate drug may be performed by dispersing drug particles in a liquid dispersion medium and applying mechanical means in the presence of grinding media to reduce the particle size of the drug to the desired effective average particle size. The particles can be reduced in size in the presence of one or more surface modifiers. Alternatively, the particles can be contacted with one or more surface modifiers after attrition. Other compounds, such as a diluent, can be added to the drug/surface modifier composition during the size reduction process. Dispersions can be manufactured continuously or in a batch mode.

Another method of forming nanoparticle dispersion is by microprecipitation. This is a method of preparing stable dispersions of drugs in the presence of one or more surface modifiers and one or more colloid stability enhancing surface active agents free of any trace toxic solvents or solubilized heavy metal impurities. Such a method comprises, for example, (1) dissolving the drug in a suitable solvent with mixing; (2) adding the formulation from step (1) with mixing to a solution comprising at least one surface modifier to form a clear solution; and (3) precipitating the formulation from step (2) with mixing using an appropriate nonsolvent. The method can be followed by removal of any formed salt, if present, by dialysis or diafiltration and concentration of the dispersion by conventional means. The resultant nanoparticulate drug dispersion can be utilized in liquid nebulizers or processed to form a dry powder for use in a DPI or pMDI.

In a non-aqueous, non-pressurized milling system, a non-aqueous liquid having a vapor pressure of about 1 atm or less at room temperature and in which the drug substance is essentially insoluble may be used as a wet milling medium to make a nanoparticulate drug composition. In such a process, a slurry of drug and surface modifier may be milled in the non-aqueous medium to generate nanoparticulate drug particles. Examples of suitable non-aqueous media include ethanol, trichloromonofluoromethane, (CFC-11), and dichlorotetrafluoroethane (CFC-114). An advantage of using CFC-11 is that it can be handled at only marginally cool room temperatures, whereas CFC-114 requires more controlled conditions to avoid evaporation. Upon completion of milling the liquid medium may be removed and recovered under vacuum or heating, resulting in a dry nanoparticulate composition. The dry composition may then be filled into a suitable container and charged with a final propellant. Exemplary final product propellants, which ideally do not contain

02 May 2016
2012212269

chlorinated hydrocarbons, include HFA-134a (tetrafluoroethane) and HFA-227 (heptafluoropropane). While non-chlorinated propellants may be preferred for environmental reasons, chlorinated propellants may also be used in this embodiment of the invention.

5 In a non-aqueous, pressurized milling system, a non-aqueous liquid medium having a vapor pressure significantly greater than 1 atm at room temperature may be used in the milling process to make nanoparticulate drug compositions. If the milling medium is a suitable halogenated hydrocarbon propellant, the resultant dispersion may be filled directly into a suitable pMDI container. Alternately, the milling medium can be removed and recovered under vacuum or heating to yield a dry nanoparticulate composition. This
10 composition can then be filled into an appropriate container and charged with a suitable propellant for use in a pMDI.

Spray drying is a process used to obtain a powder containing nanoparticulate drug particles following particle size reduction of the drug in a liquid medium. In general, spray-drying may be used when the liquid medium has a vapor pressure of less than about 1 atm at
15 room temperature. A spray-dryer is a device which allows for liquid evaporation and drug powder collection. A liquid sample, either a solution or suspension, is fed into a spray nozzle. The nozzle generates droplets of the sample within a range of about 20 to about 100 micron in diameter which are then transported by a carrier gas into a drying chamber. The carrier gas temperature is typically from about 80 to about 200° C. The droplets are subjected
20 to rapid liquid evaporation, leaving behind dry particles which are collected in a special reservoir beneath a cyclone apparatus. Smaller particles in the range down about 1 micron to about 5 microns are also possible.

If the liquid sample consists of an aqueous dispersion of nanoparticles and surface modifier, the collected product will consist of spherical aggregates of the nanoparticulate
25 drug particles. If the liquid sample consists of an aqueous dispersion of nanoparticles in which an inert diluent material was dissolved (such as lactose or mannitol), the collected product will consist of diluent (*e.g.*, lactose or mannitol) particles which contain embedded nanoparticulate drug particles. The final size of the collected product can be controlled and depends on the concentration of nanoparticulate drug and/or diluent in the liquid sample, as
30 well as the droplet size produced by the spray-dryer nozzle. Collected products may be used

02 May 2016
2012212269

in conventional DPIs for pulmonary or nasal delivery, dispersed in propellants for use in pMDIs, or the particles may be reconstituted in water for use in nebulizers.

In some instances it may be desirable to add an inert carrier to the spray-dried material to improve the metering properties of the final product. This may especially be the case when the spray dried powder is very small (less than about 5 micron) or when the intended dose is extremely small, whereby dose metering becomes difficult. In general, such carrier particles (also known as bulking agents) are too large to be delivered to the lung and simply impact the mouth and throat and are swallowed. Such carriers typically consist of sugars such as lactose, mannitol, or trehalose. Other inert materials, including polysaccharides and celluloses, may also be useful as carriers.

Spray-dried powders containing nanoparticulate drug particles may be used in conventional DPIs, dispersed in propellants for use in pMDIs, or reconstituted in a liquid medium for use with nebulizers.

For compounds that are denatured or destabilized by heat, such as compounds having a low melting point (*i.e.*, about 70 to about 150° C.), or for example, biologics, sublimation is preferred over evaporation to obtain a dry powder nanoparticulate drug composition. This is because sublimation avoids the high process temperatures associated with spray-drying. In addition, sublimation, also known as freeze-drying or lyophilization, can increase the shelf stability of drug compounds, particularly for biological products. Freeze-dried particles can also be reconstituted and used in nebulizers. Aggregates of freeze-dried nanoparticulate drug particles can be blended with either dry powder intermediates or used alone in DPIs and pMDIs for either nasal or pulmonary delivery.

Sublimation involves freezing the product and subjecting the sample to strong vacuum conditions. This allows for the formed ice to be transformed directly from a solid state to a vapor state. Such a process is highly efficient and, therefore, provides greater yields than spray-drying. The resultant freeze-dried product contains drug and modifier(s). The drug is typically present in an aggregated state and can be used for inhalation alone (either pulmonary or nasal), in conjunction with diluent materials (lactose, mannitol, etc.), in DPIs or pMDIs, or reconstituted for use in a nebulizer.

02 May 2016
2012212269**Liposomal Compositions**

In some embodiments, pirfenidone or pyridone analog compounds disclosed herein may be formulated into liposome particles, which can then be aerosolized for inhaled delivery. Lipids which are useful in the present invention can be any of a variety of lipids including both neutral lipids and charged lipids. Carrier systems having desirable properties can be prepared using appropriate combinations of lipids, targeting groups and circulation enhancers. Additionally, the compositions provided herein can be in the form of liposomes or lipid particles, preferably lipid particles. As used herein, the term "lipid particle" refers to a lipid bilayer carrier which "coats" a nucleic acid and has little or no aqueous interior. More particularly, the term is used to describe a self-assembling lipid bilayer carrier in which a portion of the interior layer comprises cationic lipids which form ionic bonds or ion-pairs with negative charges on the nucleic acid (*e.g.*, a plasmid phosphodiester backbone). The interior layer can also comprise neutral or fusogenic lipids and, in some embodiments, negatively charged lipids. The outer layer of the particle will typically comprise mixtures of lipids oriented in a tail-to-tail fashion (as in liposomes) with the hydrophobic tails of the interior layer. The polar head groups present on the lipids of the outer layer will form the external surface of the particle.

Liposomal bioactive agents can be designed to have a sustained therapeutic effect or lower toxicity allowing less frequent administration and an enhanced therapeutic index.

Liposomes are composed of bilayers that entrap the desired pharmaceutical. These can be configured as multilamellar vesicles of concentric bilayers with the pharmaceutical trapped within either the lipid of the different layers or the aqueous space between the layers.

By non-limiting example, lipids used in the compositions may be synthetic, semi-synthetic or naturally-occurring lipids, including phospholipids, tocopherols, steroids, fatty acids, glycoproteins such as albumin, negatively-charged lipids and cationic lipids.

Phospholipids include egg phosphatidylcholine (EPC), egg phosphatidylglycerol (EPG), egg phosphatidylinositol (EPI), egg phosphatidylserine (EPS), phosphatidylethanolamine (EPE), and egg phosphatidic acid (EPA); the soya counterparts, soy phosphatidylcholine (SPC); SPG, SPS, SPI, SPE, and SPA; the hydrogenated egg and soya counterparts (*e.g.*, HEPC, HSPC), other phospholipids made up of ester linkages of fatty acids in the 2 and 3 of glycerol positions containing chains of 12 to 26 carbon atoms and different head groups in the 1

02 May 2016
2012212269

position of glycerol that include choline, glycerol, inositol, serine, ethanolamine, as well as the corresponding phosphatidic acids. The chains on these fatty acids can be saturated or unsaturated, and the phospholipid can be made up of fatty acids of different chain lengths and different degrees of unsaturation. In particular, the compositions of the formulations can include dipalmitoylphosphatidylcholine (DPPC), a major constituent of naturally-occurring lung surfactant as well as dioleoylphosphatidylcholine (DOPC) and dioleoylphosphatidylglycerol (DOPG). Other examples include dimyristoylphosphatidylcholine (DMPC) and dimyristoylphosphatidylglycerol (DMPG) dipalmitoylphosphatidylcholine (DPPC) and dipalmitoylphosphatidylglycerol (DPPG), distearoylphosphatidylcholine (DSPC) and distearoylphosphatidylglycerol (DSPG), dioleoylphosphatidylethanolamine (DOPE) and mixed phospholipids like palmitoylstearylphosphatidylcholine (PSPC) and palmitoylstearylphosphatidylglycerol (PSPG), and single acylated phospholipids like mono-oleoyl-phosphatidylethanolamine (MOPE).

In a preferred embodiment, PEG-modified lipids are incorporated into the compositions of the present invention as the aggregation-preventing agent. The use of a PEG-modified lipid positions bulky PEG groups on the surface of the liposome or lipid carrier and prevents binding of DNA to the outside of the carrier (thereby inhibiting cross-linking and aggregation of the lipid carrier). The use of a PEG-ceramide is often preferred and has the additional advantages of stabilizing membrane bilayers and lengthening circulation lifetimes. Additionally, PEG-ceramides can be prepared with different lipid tail lengths to control the lifetime of the PEG-ceramide in the lipid bilayer. In this manner, "programmable" release can be accomplished which results in the control of lipid carrier fusion. For example, PEG-ceramides having C₂₀ -acyl groups attached to the ceramide moiety will diffuse out of a lipid bilayer carrier with a half-life of 22 hours. PEG-ceramides having C₁₄ - and C₈ -acyl groups will diffuse out of the same carrier with half-lives of 10 minutes and less than 1 minute, respectively. As a result, selection of lipid tail length provides a composition in which the bilayer becomes destabilized (and thus fusogenic) at a known rate. Though less preferred, other PEG-lipids or lipid-polyoxyethylene conjugates are useful in the present compositions. Examples of suitable PEG-modified lipids include PEG-modified phosphatidylethanolamine and phosphatidic acid, PEG-modified diacylglycerols

02 May 2016
2012212269

and dialkylglycerols, PEG-modified dialkylamines and PEG-modified 1,2-diacyloxypropan-3-amines. Particularly preferred are PEG-ceramide conjugates (*e.g.*, PEG-Cer-C₈, PEG-Cer-C₁₄ or PEG-Cer-C₂₀) which are described in U.S. Pat. No. 5,820,873, incorporated herein by reference.

5 The compositions of the present invention can be prepared to provide liposome compositions which are about 50 nm to about 400 nm in diameter. One with skill in the art will understand that the size of the compositions can be larger or smaller depending upon the volume which is encapsulated. Thus, for larger volumes, the size distribution will typically be from about 80 nm to about 300 nm.

10 Surface Modifiers

Pirfenidone or pyridone analog compounds disclosed herein may be prepared in a pharmaceutical composition with suitable surface modifiers which may be selected from known organic and inorganic pharmaceutical excipients. Such excipients include low molecular weight oligomers, polymers, surfactants and natural products. Preferred surface
15 modifiers include nonionic and ionic surfactants. Two or more surface modifiers can be used in combination.

Representative examples of surface modifiers include cetyl pyridinium chloride, gelatin, casein, lecithin (phosphatides), dextran, glycerol, gum acacia, cholesterol, tragacanth, stearic acid, benzalkonium chloride, calcium stearate, glycerol monostearate, cetostearyl
20 alcohol, cetomacrogol emulsifying wax, sorbitan esters, polyoxyethylene alkyl ethers (*e.g.*, macrogol ethers such as cetomacrogol 1000), polyoxyethylene castor oil derivatives, polyoxyethylene sorbitan fatty acid esters (*e.g.*, the commercially available Tweens™, such as *e.g.*, Tween 20™, and Tween 80™, (ICI Specialty Chemicals)); polyethylene glycols (*e.g.*, Carbowax 3350™, and 1450™, and Carbopol 934™, (Union Carbide)), dodecyl trimethyl
25 ammonium bromide, polyoxyethylenestearates, colloidal silicon dioxide, phosphates, sodium dodecylsulfate, carboxymethylcellulose calcium, hydroxypropyl cellulose (HPC, HPC-SL, and HPC-L), hydroxypropyl methylcellulose (HPMC), carboxymethylcellulose sodium, methylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethyl-
cellulose phthalate, noncrystalline cellulose, magnesium aluminum silicate, triethanolamine,
30 polyvinyl alcohol (PVA), polyvinylpyrrolidone (PVP), 4-(1,1,3,3-tetraamethylbutyl)-phenol polymer with ethylene oxide and formaldehyde (also known as tyloxapol, superione, and

02 May 2016
2012212269

triton), poloxamers (*e.g.*, Pluronic F68™, and F108™, which are block copolymers of ethylene oxide and propylene oxide); poloxamnines (*e.g.*, Tetronic 908™, also known as Poloxamine 908™, which is a tetrafunctional block copolymer derived from sequential addition of propylene oxide and ethylene oxide to ethylenediamine (BASF Wyandotte Corporation, Parsippany, N.J.)); a charged phospholipid such as dimyristoyl phosphatidyl glycerol, dioctylsulfosuccinate (DOSS); Tetronic 1508™; (T-1508) (BASF Wyandotte Corporation), dialkylesters of sodium sulfosuccinic acid (*e.g.*, Aerosol OT™, which is a dioctyl ester of sodium sulfosuccinic acid (American Cyanamid)); Duponol P™, which is a sodium lauryl sulfate (DuPont); Tritons X-200™, which is an alkyl aryl polyether sulfonate (Rohm and Haas); Crodestas F-110™, which is a mixture of sucrose stearate and sucrose distearate (Croda Inc.); p-isononylphenoxypoly-(glycidol), also known as Olin-log™, or Surfactant 10-G™, (Olin Chemicals, Stamford, Conn.); Crodestas SL-40™, (Croda, Inc.); and SA9OHCO, which is C₁₈ H₃₇ CH₂ (CON(CH₃)-CH₂ (CHOH)₄ (CH₂ OH)₂ (Eastman Kodak Co.); decanoyl-N-methylglucamide; n-decyl β-D-glucopyranoside; n-decyl β-D-maltopyranoside; n-dodecyl β-D-glucopyranoside; n-dodecyl β-D-maltoside; heptanoyl-N-methylglucamide; n-heptyl-β-D-glucopyranoside; n-heptyl β-D-thioglucoside; n-hexyl β-D-glucopyranoside; nonanoyl-N-methylglucamide; n-nonyl β-D-glucopyranoside; octanoyl-N-methylglucarmide; n-octyl-β-D-glucopyranoside; octyl β-D-thioglucopyranoside; and the like. Tyloxapol is a particularly preferred surface modifier for the pulmonary or intranasal delivery of steroids, even more so for nebulization therapies.

Examples of surfactants for use in the solutions disclosed herein include, but are not limited to, ammonium laureth sulfate, cetamine oxide, cetrimonium chloride, cetyl alcohol, cetyl myristate, cetyl palmitate, cocamide DEA, cocamidopropyl betaine, cocamidopropylamine oxide, cocamide MEA, DEA lauryl sulfate, di-stearyl phthalic acid amide, dicetyl dimethyl ammonium chloride, dipalmitoylethyl hydroxethylmonium, disodium laureth sulfosuccinate, di(hydrogenated) tallow phthalic acid, glyceryl dilaurate, glyceryl distearate, glyceryl oleate, glyceryl stearate, isopropyl myristate nf, isopropyl palmitate nf, lauramide DEA, lauramide MEA, lauramide oxide, myristamine oxide, octyl isononanoate, octyl palmitate, octyldodecyl neopentanoate, olealkonium chloride, PEG-2 stearate, PEG-32 glyceryl caprylate/caprinate, PEG-32 glyceryl stearate, PEG-4 and PEG-150 stearate & distearate, PEG-4 to PEG-150 laurate & dilaurate, PEG-4 to PEG-150 oleate & dioleate,

02 May 2016
2012212269

PEG-7 glyceryl cocoate, PEG-8 beeswax, propylene glycol stearate, sodium C14-16 olefin sulfonate, sodium lauryl sulfoacetate, sodium lauryl sulphate, sodium trideceth sulfate, stearalkonium chloride, stearamide oxide, TEA-dodecylbenzene sulfonate, TEA lauryl sulfate

Most of these surface modifiers are known pharmaceutical excipients and are described in detail in the Handbook of Pharmaceutical Excipients, published jointly by the American Pharmaceutical Association and The Pharmaceutical Society of Great Britain (The Pharmaceutical Press, 1986), specifically incorporated by reference. The surface modifiers are commercially available and/or can be prepared by techniques known in the art. The relative amount of drug and surface modifier can vary widely and the optimal amount of the surface modifier can depend upon, for example, the particular drug and surface modifier selected, the critical micelle concentration of the surface modifier if it forms micelles, the hydrophilic-lipophilic-balance (HLB) of the surface modifier, the melting point of the surface modifier, the water solubility of the surface modifier and/or drug, the surface tension of water solutions of the surface modifier, etc.

In the present invention, the optimal ratio of drug to surface modifier is ~0.1% to ~99.9% pirfenidone or pyridone analog compound, more preferably about 10% to about 90%.

Microspheres

Microspheres can be used for pulmonary delivery of pirfenidone or pyridone analog compounds by first adding an appropriate amount of drug compound to be solubilized in water. For example, an aqueous pirfenidone or pyridone analog compound solution may be dispersed in methylene chloride containing a predetermined amount (0.1-1% w/v) of poly(DL-lactide-co-glycolide) (PLGA) by probe sonication for 1-3 min on an ice bath. Separately, a pirfenidone or pyridone analog compound may be solubilized in methylene chloride containing PLGA (0.1-1% w/v). The resulting water-in-oil primary emulsion or the polymer/drug solution will be dispersed in an aqueous continuous phase consisting of 1-2% polyvinyl alcohol (previously cooled to 4°C) by probe sonication for 3-5 min on an ice bath. The resulting emulsion will be stirred continuously for 2-4 hours at room temperature to evaporate methylene chloride. Microparticles thus formed will be separated from the continuous phase by centrifuging at 8000-10000 rpm for 5-10 min. Sedimented particles will be washed thrice with distilled water and freeze dried. Freeze-dried pirfenidone or pyridone analog compound microparticles will be stored at -20°C.

02 May 2016
2012212269

By non-limiting example, a spray drying approach will be employed to prepare pirfenidone or pyridone analog compound microspheres. An appropriate amount of pirfenidone or pyridone analog compound will be solubilized in methylene chloride containing PLGA (0.1-1%). This solution will be spray dried to obtain the microspheres.

By non-limiting example, pirfenidone or pyridone analog compound microparticles will be characterized for size distribution (requirement: 90% <5 μm , 95% <10 μm), shape, drug loading efficiency and drug release using appropriate techniques and methods.

By non-limiting example, this approach may also be used to sequester and improve the water solubility of solid, AUC shape-enhancing formulations, such as low-solubility pirfenidone or pyridone analog compounds or salt forms for nanoparticle-based formulations.

A certain amount of pirfenidone or pyridone analog compound can be first dissolved in the minimal quantity of ethanol 96% necessary to maintain the fluoroquinolone in solution when diluted with water from 96 to 75%. This solution can then be diluted with water to obtain a 75% ethanol solution and then a certain amount of paracetamol can be added to obtain the following w/w drug/polymer ratios: 1:2, 1:1, 2:1, 3:1, 4:1, 6:1, 9:1, and 19:1. These final solutions are spray-dried under the following conditions: feed rate, 15 mL/min; inlet temperature, 110°C; outlet temperature, 85°C; pressure 4 bar and throughput of drying air, 35m³/hr. Powder is then collected and stored under vacuum in a dessiccator.

Solid Lipid Particles

Preparation of pirfenidone or pyridone analog compound solid lipid particles may involve dissolving the drug in a lipid melt (phospholipids such as phosphatidyl choline and phosphatidyl serine) maintained at least at the melting temperature of the lipid, followed by dispersion of the drug-containing melt in a hot aqueous surfactant solution (typically 1-5% w/v) maintained at least at the melting temperature of the lipid. The coarse dispersion will be homogenized for 1-10 min using a Microfluidizer® to obtain a nanoemulsion. Cooling the nanoemulsion to a temperature between 4-25°C will re-solidify the lipid, leading to formation of solid lipid nanoparticles. Optimization of formulation parameters (type of lipid matrix, surfactant concentration and production parameters) will be performed so as to achieve a prolonged drug delivery. By non-limiting example, this approach may also be used to sequester and improve the water solubility of solid, AUC shape-enhancing formulations, such

02 May 2016
2012212269

as low-solubility pirfenidone or pyridone analog compounds or salt forms for nanoparticle-based formulations.

Melt-Extrusion AUC Shape-Enhancing Formulation

Melt-Extrusion AUC shape-enhancing pirfenidone or pyridone analog compound
5 formulations may be preparation by dissolving the drugs in micelles by adding surfactants or preparing micro-emulsion, forming inclusion complexes with other molecules such as cyclodextrins, forming nanoparticles of the drugs, or embedding the amorphous drugs in a polymer matrix. Embedding the drug homogeneously in a polymer matrix produces a solid dispersion. Solid dispersions can be prepared in two ways: the solvent method and the hot
10 melt method. The solvent method uses an organic solvent wherein the drug and appropriate polymer are dissolved and then (spray) dried. The major drawbacks of this method are the use of organic solvents and the batch mode production process. The hot melt method uses heat in order to disperse or dissolve the drug in an appropriate polymer. The melt-extrusion process is an optimized version of the hot melt method. The advantage of the melt-extrusion
15 approach is lack of organic solvent and continuous production process. As the melt-extrusion is a novel pharmaceutical technique, the literature dealing with it is limited. The technical set-up involves a mixture and extrusion of pirfenidone or pyridone analog compound, hydroxypropyl-b-cyclodextrin (HP-b-CD), and hydroxypropylmethylcellulose (HPMC), in order to, by non-limiting example create a AUC shape-enhancing formulation of pirfenidone
20 or pyridone analog compound. Cyclodextrin is a toroidal-shaped molecule with hydroxyl groups on the outer surface and a cavity in the center. Cyclodextrin sequesters the drug by forming an inclusion complex. The complex formation between cyclodextrins and drugs has been investigated extensively. It is known that water-soluble polymer interacts with cyclodextrin and drug in the course of complex formation to form a stabilized complex of
25 drug and cyclodextrin co-complexed with the polymer. This complex is more stable than the classic cyclodextrin-drug complex. As one example, HPMC is water soluble; hence using this polymer with HP-b-CD in the melt is expected to create an aqueous soluble AUC shape-enhancing formulation. By non-limiting example, this approach may also be used to sequester and improve the water solubility of solid, AUC shape-enhancing formulations, such
30 as low-solubility pirfenidone or pyridone analog compounds or salt forms for nanoparticle-based formulations.

02 May 2016
2012212269**Co-Precipitates**

Co-precipitate pirfenidone or pyridone analog compound formulations may be prepared by formation of co-precipitates with pharmacologically inert, polymeric materials. It has been demonstrated that the formation of molecular solid dispersions or co-precipitates to create an AUC shape-enhancing formulations with various water-soluble polymers can significantly slow their *in vitro* dissolution rates and/or *in vivo* absorption. In preparing powdered products, grinding is generally used for reducing particle size, since the dissolution rate is strongly affected by particle size. Moreover, a strong force (such as grinding) may increase the surface energy and cause distortion of the crystal lattice as well as reducing particle size. Co-grinding drug with hydroxypropylmethylcellulose, b-cyclodextrin, chitin and chitosan, crystalline cellulose, and gelatin, may enhance the dissolution properties such that AUC shape-enhancement is obtained for otherwise readily bioavailable pirfenidone or pyridone analog compounds. By non-limiting example, this approach may also be used to sequester and improve the water solubility of solid, AUC shape-enhancing formulations, such as low-solubility pirfenidone or pyridone analog compounds or salt forms for nanoparticle-based formulations.

Dispersion-Enhancing Peptides

Compositions may include one or more di- or tripeptides containing two or more leucine residues. By further non-limiting example, U.S. Patent No. 6,835,372 disclosing dispersion-enhancing peptides, is hereby incorporated by reference in its entirety. This patent describes the discovery that di-leucyl-containing dipeptides (*e.g.*, dileucine) and tripeptides are superior in their ability to increase the dispersibility of powdered composition.

In another embodiment, highly dispersible particles including an amino acid are administered. Hydrophobic amino acids are preferred. Suitable amino acids include naturally occurring and non-naturally occurring hydrophobic amino acids. Some naturally occurring hydrophobic amino acids, including but not limited to, non-naturally occurring amino acids include, for example, beta-amino acids. Both D, L and racemic configurations of hydrophobic amino acids can be employed. Suitable hydrophobic amino acids can also include amino acid analogs. As used herein, an amino acid analog includes the D or L configuration of an amino acid having the following formula: --NH--CHR--CO--, wherein R is an aliphatic group, a substituted aliphatic group, a benzyl group, a substituted benzyl

02 May 2016
2012212269

group, an aromatic group or a substituted aromatic group and wherein R does not correspond to the side chain of a naturally-occurring amino acid. As used herein, aliphatic groups include straight chained, branched or cyclic C1-C8 hydrocarbons which are completely saturated, which contain one or two heteroatoms such as nitrogen, oxygen or sulfur and/or which contain one or more units of desaturation. Aromatic groups include carbocyclic aromatic groups such as phenyl and naphthyl and heterocyclic aromatic groups such as imidazolyl, indolyl, thienyl, furanyl, pyridyl, pyranal, oxazolyl, benzothienyl, benzofuranyl, quinolinyl, isoquinolinyl and acridintyl.

Suitable substituents on an aliphatic, aromatic or benzyl group include --OH, halogen (--Br, --Cl, --I and --F)--O(aliphatic, substituted aliphatic, benzyl, substituted benzyl, aryl or substituted aryl group), --CN, --NO₂, --COOH, --NH₂, --NH(aliphatic group, substituted aliphatic, benzyl, substituted benzyl, aryl or substituted aryl group), --N(aliphatic group, substituted aliphatic, benzyl, substituted benzyl, aryl or substituted aryl group)₂, --COO(aliphatic group, substituted aliphatic, benzyl, substituted benzyl, aryl or substituted aryl group), --CONH₂, --CONH(aliphatic, substituted aliphatic group, benzyl, substituted benzyl, aryl or substituted aryl group)), --SH, --S(aliphatic, substituted aliphatic, benzyl, substituted benzyl, aromatic or substituted aromatic group) and --NH--C(.dbd.NH)--NH₂. A substituted benzylic or aromatic group can also have an aliphatic or substituted aliphatic group as a substituent. A substituted aliphatic group can also have a benzyl, substituted benzyl, aryl or substituted aryl group as a substituent. A substituted aliphatic, substituted aromatic or substituted benzyl group can have one or more substituents. Modifying an amino acid substituent can increase, for example, the lypophilicity or hydrophobicity of natural amino acids which are hydrophilic.

A number of the suitable amino acids, amino acids analogs and salts thereof can be obtained commercially. Others can be synthesized by methods known in the art.

Hydrophobicity is generally defined with respect to the partition of an amino acid between a nonpolar solvent and water. Hydrophobic amino acids are those acids which show a preference for the nonpolar solvent. Relative hydrophobicity of amino acids can be expressed on a hydrophobicity scale on which glycine has the value 0.5. On such a scale, amino acids which have a preference for water have values below 0.5 and those that have a preference for nonpolar solvents have a value above 0.5. As used herein, the term

02 May 2016
2012212269

hydrophobic amino acid refers to an amino acid that, on the hydrophobicity scale, has a value greater or equal to 0.5, in other words, has a tendency to partition in the nonpolar acid which is at least equal to that of glycine.

Examples of amino acids which can be employed include, but are not limited to:
5 glycine, proline, alanine, cysteine, methionine, valine, leucine, tyrosine, isoleucine, phenylalanine, tryptophan. Preferred hydrophobic amino acids include leucine, isoleucine, alanine, valine, phenylalanine and glycine. Combinations of hydrophobic amino acids can also be employed. Furthermore, combinations of hydrophobic and hydrophilic (preferentially partitioning in water) amino acids, where the overall combination is hydrophobic, can also be
10 employed.

The amino acid can be present in the particles of the invention in an amount of at least 10 weight %. Preferably, the amino acid can be present in the particles in an amount ranging from about 20 to about 80 weight %. The salt of a hydrophobic amino acid can be present in the particles of the invention in an amount of at least 10 weight percent. Preferably, the
15 amino acid salt is present in the particles in an amount ranging from about 20 to about 80 weight %. In preferred embodiments the particles have a tap density of less than about 0.4 g/cm³.

Methods of forming and delivering particles which include an amino acid are described in U.S. Patent No. 6,586,008, entitled Use of Simple Amino Acids to Form Porous
20 Particles During Spray Drying, the teachings of which are incorporated herein by reference in their entirety.

Proteins/Amino Acids

Protein excipients may include albumins such as human serum albumin (HSA), recombinant human albumin (rHA), gelatin, casein, hemoglobin, and the like. Suitable
25 amino acids (outside of the dileucyl-peptides of the invention), which may also function in a buffering capacity, include alanine, glycine, arginine, betaine, histidine, glutamic acid, aspartic acid, cysteine, lysine, leucine, isoleucine, valine, methionine, phenylalanine, aspartame, tyrosine, tryptophan, and the like. Preferred are amino acids and polypeptides that function as dispersing agents. Amino acids falling into this category include hydrophobic
30 amino acids such as leucine, valine, isoleucine, tryptophan, alanine, methionine, phenylalanine, tyrosine, histidine, and proline. Dispersibility-enhancing peptide excipients

include dimers, trimers, tetramers, and pentamers comprising one or more hydrophobic amino acid components such as those described above.

Carbohydrates

By non-limiting example, carbohydrate excipients may include monosaccharides such as fructose, maltose, galactose, glucose, D-mannose, sorbose, and the like; disaccharides, such as lactose, sucrose, trehalose, cellobiose, and the like; polysaccharides, such as raffinose, melezitose, maltodextrins, dextrans, starches, and the like; and alditols, such as mannitol, xylitol, maltitol, lactitol, xylitol sorbitol (glucitol), pyranosyl sorbitol, myoinositol, isomalt, trehalose and the like.

Polymers

By non-limiting example, compositions may also include polymeric excipients/additives, *e.g.*, polyvinylpyrrolidones, derivatized celluloses such as hydroxymethylcellulose, hydroxyethylcellulose, and hydroxypropylmethylcellulose, Ficolls (a polymeric sugar), hydroxyethylstarch, dextrans (by non-limiting example cyclodextrins may include, 2-hydroxypropyl-beta-cyclodextrin, 2-hydroxypropyl-gamma-cyclodextrin, randomly methylated beta-cyclodextrin, dimethyl-alpha-cyclodextrin, dimethyl-beta-cyclodextrin, maltosyl-alpha-cyclodextrin, glucosyl-1-alpha-cyclodextrin, glucosyl-2-alpha-cyclodextrin, alpha-cyclodextrin, beta-cyclodextrin, gamma-cyclodextrin, and sulfobutylether-beta-cyclodextrin), polyethylene glycols, and pectin may also be used.

Highly dispersible particles administered comprise a bioactive agent and a biocompatible, and preferably biodegradable polymer, copolymer, or blend. The polymers may be tailored to optimize different characteristics of the particle including: i) interactions between the agent to be delivered and the polymer to provide stabilization of the agent and retention of activity upon delivery; ii) rate of polymer degradation and, thereby, rate of drug release profiles; iii) surface characteristics and targeting capabilities via chemical modification; and iv) particle porosity.

Surface eroding polymers such as polyanhydrides may be used to form the particles. For example, polyanhydrides such as poly[(p-carboxyphenoxy)hexane anhydride] (PCPH) may be used. Biodegradable polyanhydrides are described in U.S. Pat. No. 4,857,311. Bulk eroding polymers such as those based on polyesters including poly(hydroxy acids) also can be used. For example, polyglycolic acid (PGA), polylactic acid (PLA), or copolymers

02 May 2016

2012212269

thereof may be used to form the particles. The polyester may also have a charged or functionalizable group, such as an amino acid. In a preferred embodiment, particles with controlled release properties can be formed of poly(D,L-lactic acid) and/or poly(DL-lactic-co-glycolic acid) ("PLGA") which incorporate a surfactant such as dipalmitoyl phosphatidylcholine (DPPC).

Other polymers include polyamides, polycarbonates, polyalkylenes such as polyethylene, polypropylene, poly(ethylene glycol), poly(ethylene oxide), poly(ethylene terephthalate), poly vinyl compounds such as polyvinyl alcohols, polyvinyl ethers, and polyvinyl esters, polymers of acrylic and methacrylic acids, celluloses and other polysaccharides, and peptides or proteins, or copolymers or blends thereof. Polymers may be selected with or modified to have the appropriate stability and degradation rates *in vivo* for different controlled drug delivery applications.

Highly dispersible particles can be formed from functionalized polyester graft copolymers, as described in Hrkach et al., *Macromolecules*, 28: 4736-4739 (1995); and Hrkach et al., "Poly(L-Lactic acid-co-amino acid) Graft Copolymers: A Class of Functional Biodegradable Biomaterials" in *Hydrogels and Biodegradable Polymers for Bioapplications*, ACS Symposium Series No. 627, Raphael M, Ottenbrite et al., Eds., American Chemical Society, Chapter 8, pp. 93-101, 1996.

In a preferred embodiment of the invention, highly dispersible particles including a bioactive agent and a phospholipid are administered. Examples of suitable phospholipids include, among others, phosphatidylcholines, phosphatidylethanolamines, phosphatidylglycerols, phosphatidylserines, phosphatidylinositols and combinations thereof. Specific examples of phospholipids include but are not limited to phosphatidylcholines dipalmitoyl phosphatidylcholine (DPPC), dipalmitoyl phosphatidylethanolamine (DPPE), distearoyl phosphatidylcholine (DSPC), dipalmitoyl phosphatidyl glycerol (DPPG) or any combination thereof. Other phospholipids are known to those skilled in the art. In a preferred embodiment, the phospholipids are endogenous to the lung.

The phospholipid, can be present in the particles in an amount ranging from about 0 to about 90 weight %. More commonly it can be present in the particles in an amount ranging from about 10 to about 60 weight %.

02 May 2016
2012212269

In another embodiment of the invention, the phospholipids or combinations thereof are selected to impart controlled release properties to the highly dispersible particles. The phase transition temperature of a specific phospholipid can be below, about or above the physiological body temperature of a patient. Preferred phase transition temperatures range from 30 degrees C to 50 degrees C (*e.g.*, within +/-10 degrees of the normal body temperature of patient). By selecting phospholipids or combinations of phospholipids according to their phase transition temperature, the particles can be tailored to have controlled release properties. For example, by administering particles which include a phospholipid or combination of phospholipids which have a phase transition temperature higher than the patient's body temperature, the release of dopamine precursor, agonist or any combination of precursors and/or agonists can be slowed down. On the other hand, rapid release can be obtained by including in the particles phospholipids having lower transition temperatures.

Taste Masking, Flavor, Other

As also described above, pirfenidone or pyridone analog compound formulations disclosed herein and related compositions, may further include one or more taste-masking agents such as flavoring agents, inorganic salts (*e.g.*, sodium chloride), sweeteners, antioxidants, antistatic agents, surfactants (*e.g.*, polysorbates such as "TWEEN 20" and "TWEEN 80"), sorbitan esters, saccharin (*e.g.*, sodium saccharin or other saccharin forms, which as noted elsewhere herein may be present in certain embodiments at specific concentrations or at specific molar ratios relative to a pyridone analog compound such as pirfenidone), bicarbonate, cyclodextrins, lipids (*e.g.*, phospholipids such as lecithin and other phosphatidylcholines, phosphatidylethanolamines), fatty acids and fatty esters, steroids (*e.g.*, cholesterol), and chelating agents (*e.g.*, EDTA, zinc and other such suitable cations). Other pharmaceutical excipients and/or additives suitable for use in the compositions according to the invention are listed in "Remington: The Science & Practice of Pharmacy", 19th ed., Williams & Williams, (1995), and in the "Physician's Desk Reference", 52nd ed., Medical Economics, Montvale, N.J. (1998).

By way of non-limiting example, taste-masking agents in pirfenidone or pyridone analog compound formulations, may include the use of flavorings, sweeteners, and other various coating strategies, for instance, sugars such as sucrose, dextrose, and lactose, carboxylic acids, menthol, amino acids or amino acid derivatives such as arginine, lysine, and

02 May 2016
2012212269

monosodium glutamate, and/or synthetic flavor oils and flavoring aromatics and/or natural oils, extracts from plants, leaves, flowers, fruits, etc. and combinations thereof. These may include cinnamon oils, oil of wintergreen, peppermint oils, clover oil, bay oil, anise oil, eucalyptus, vanilla, citrus oil such as lemon oil, orange oil, grape and grapefruit oil, fruit

5 essences including apple, peach, pear, strawberry, raspberry, cherry, plum, pineapple, apricot, etc. Additional sweeteners include sucrose, dextrose, aspartame (Nutrasweet®), acesulfame-K, sucralose and saccharin (*e.g.*, sodium saccharin or other saccharin forms, which as noted elsewhere herein may be present in certain embodiments at specific concentrations or at specific molar ratios relative to a pyridone analog compound such as pirfenidone), organic

10 acids (by non-limiting example citric acid and aspartic acid). Such flavors may be present at from about 0.05 to about 4 percent by weight, and may be present at lower or higher amounts as a factor of one or more of potency of the effect on flavor, solubility of the flavorant, effects of the flavorant on solubility or other physicochemical or pharmacokinetic properties of other formulation components, or other factors.

15 Another approach to improve or mask the unpleasant taste of an inhaled drug may be to decrease the drug's solubility, *e.g.*, drugs must dissolve to interact with taste receptors. Hence, to deliver solid forms of the drug may avoid the taste response and result in the desired improved taste affect. Non-limiting methods to decrease solubility of a pirfenidone or pyridone analog compound solubility are described herein, for example, through the use in

20 formulation of particular salt forms of pyridone analog compound, such as complexation with xinafoic acid, oleic acid, stearic acid and/or pamoic acid. Additional co-precipitating agents include dihydropyridines and a polymer such as polyvinyl pyrrolidone.

Moreover, taste-masking may be accomplished by creation of lipophilic vesicles.

Additional coating or capping agents include dextrans (by non-limiting example

25 cyclodextrins may include, 2-hydroxypropyl-beta-cyclodextrin, 2-hydroxypropyl-gamma-cyclodextrin, randomly methylated beta-cyclodextrin, dimethyl-alpha-cyclodextrin, dimethyl-beta-cyclodextrin, maltosyl-alpha-cyclodextrin, glucosyl-1-alpha-cyclodextrin, glucosyl-2-alpha-cyclodextrin, alpha-cyclodextrin, beta-cyclodextrin, gamma-cyclodextrin, and sulfobutylether-beta-cyclodextrin), modified celluloses such as ethyl cellulose, methyl

30 cellulose, hydroxypropyl cellulose, hydroxyl propyl methyl cellulose, polyalkylene glycols, polyalkylene oxides, sugars and sugar alcohols, waxes, shellacs, acrylics and mixtures

02 May 2016

2012212269

thereof. By non-limiting example, other methods to deliver non-dissolved forms of a pirfenidone or pyridone analog compound according to certain embodiments or, in other embodiments, non-dissolved forms of a pirfenidone or pyridone analog compound, are to administer the drug alone or in a simple, non-solubility affecting formulation, such as a crystalline micronized, dry powder, spray-dried, and/or nanosuspension formulation.

An alternative according to certain other preferred embodiments is to include taste-modifying agents in the pirfenidone or pyridone analog compound formulation. These embodiments contemplate including in the formulation a taste-masking substance that is mixed with, coated onto or otherwise combined with the active medicament pirfenidone or pyridone analog compound or salt thereof. Inclusion of one or more such agents in these formulations may also serve to improve the taste of additional pharmacologically active compounds that are included in the formulations in addition to the pirfenidone or pyridone analog compound, *e.g.*, a mucolytic agent. Non-limiting examples of such taste-modifying substances include acid phospholipids, lysophospholipid, tocopherol polyethyleneglycol succinate, and embonic acid (pamoate). Many of these agents can be used alone or in combination with pirfenidone or pyridone analog compound (or a salt thereof) or, in separate embodiments, pirfenidone or pyridone analog compound for aerosol administration.

Mucolytic Agents

Methods to produce formulations that combine agents to reduce sputum viscosity during aerosol treatment with a pirfenidone or pyridone analog compound include the following. These agents can be prepared in fixed combination or be administered in succession with aerosol pirfenidone or pyridone analog compound therapy.

The most commonly prescribed agent is N-acetylcysteine (NAC), which depolymerizes mucus *in vitro* by breaking disulphide bridges between macromolecules. It is assumed that such reduction of sputum tenacity facilitates its removal from the respiratory tract. In addition, NAC may act as an oxygen radical scavenger. NAC can be taken either orally or by inhalation. Differences between these two methods of administration have not been formally studied. After oral administration, NAC is reduced to cysteine, a precursor of the antioxidant glutathione, in the liver and intestine. The antioxidant properties could be useful in preventing decline of lung function in cystic fibrosis (CF), chronic obstructive pulmonary disease (COPD) or pulmonary fibrotic diseases (*e.g.*, idiopathic pulmonary

02 May 2016
2012212269

fibrosis). Nebulized NAC is commonly prescribed to patients with CF, in particular in continental Europe, in order to improve expectoration of sputum by reducing its tenacity. The ultimate goal of this is to slow down the decline of lung function in CF.

5 L-lysine-N-acetylcysteinate (ACC) or Nacystelyn (NAL) is a novel mucoactive agent possessing mucolytic, antioxidant, and anti-inflammatory properties. Chemically, it is a salt of ACC. This drug appears to present an activity superior to its parent molecule ACC because of a synergistic mucolytic activity of L-lysine and ACC. Furthermore, its almost neutral pH (6.2) allows its administration in the lungs with a very low incidence of bronchospasm, which is not the case for the acidic ACC (pH 2.2). NAL is difficult to
10 formulate in an inhaled form because the required lung dose is very high (approximately 2 mg) and the micronized drug is sticky and cohesive and it is thus problematic to produce a redispersable formulation. NAL was first developed as a chlorofluorocarbon (CFC) containing metered-dose inhaler (MDI) because this form was the easiest and the fastest to develop to begin the preclinical and the first clinical studies. NAL MDI delivered 2 mg per
15 puff, from which approximately 10% was able to reach the lungs in healthy volunteers. One major inconvenience of this formulation was patient compliance because as many as 12 puffs were necessary to obtain the required dose. Furthermore, the progressive removal of CFC gases from medicinal products combined with the problems of coordination met in a large proportion of the patient population (12) have led to the development of a new galenical form
20 of NAL. A dry powder inhaler (DPI) formulation was chosen to resolve the problems of compliance with MDIs and to combine it with an optimal, reproducible, and comfortable way to administer the drug to the widest possible patient population, including young children.

The DPI formulation of NAL involved the use of a nonconventional lactose (usually reserved for direct compression of tablets), namely, a roller-dried (RD) anhydrous β -lactose.
25 When tested in vitro with a monodose DPI device, this powder formulation produces a fine particle fraction (FPF) of at least 30% of the nominal dose, namely three times higher than that with MDIs. This approach may be used in combination with a pirfenidone or pyridone analog compound for either co-administration or fixed combination therapy.

In addition to mucolytic activity, excessive neutrophil elastase activity within airways
30 of cystic fibrosis (CF) patients results in progressive lung damage. Disruption of disulfide bonds on elastase by reducing agents may modify its enzymatic activity. Three naturally

02 May 2016
2012212269

occurring dithiol reducing systems were examined for their effects on elastase activity: 1) Escherichia coli thioredoxin (Trx) system, 2) recombinant human thioredoxin (rhTrx) system, and 3) dihydrolipoic acid (DHLA). The Trx systems consisted of Trx, Trx reductase, and NADPH. As shown by spectrophotometric assay of elastase activity, the two Trx systems and DHLA inhibited purified human neutrophil elastase as well as the elastolytic activity present in the soluble phase (sol) of CF sputum. Removal of any of the three Trx system constituents prevented inhibition. Compared with the monothiols N-acetylcysteine and reduced glutathione, the dithiols displayed greater elastase inhibition. To streamline Trx as an investigational tool, a stable reduced form of rhTrx was synthesized and used as a single component. Reduced rhTrx inhibited purified elastase and CF sputum sol elastase without NADPH or Trx reductase. Because Trx and DHLA have mucolytic effects, we investigated changes in elastase activity after mucolytic treatment. Unprocessed CF sputum was directly treated with reduced rhTrx, the Trx system, DHLA, or DNase. The Trx system and DHLA did not increase elastase activity, whereas reduced rhTrx treatment increased sol elastase activity by 60%. By contrast, the elastase activity after DNase treatment increased by 190%. The ability of Trx and DHLA to limit elastase activity combined with their mucolytic effects makes these compounds potential therapies for CF.

In addition, bundles of F-actin and DNA present in the sputum of cystic fibrosis (CF) patients but absent from normal airway fluid contribute to the altered viscoelastic properties of sputum that inhibit clearance of infected airway fluid and exacerbate the pathology of CF. One approach to alter these adverse properties is to remove these filamentous aggregates using DNase to enzymatically depolymerize DNA to constituent monomers and gelsolin to sever F-actin to small fragments. The high densities of negative surface charge on DNA and F-actin suggest that the bundles of these filaments, which alone exhibit a strong electrostatic repulsion, may be stabilized by multivalent cations such as histones, antimicrobial peptides, and other positively charged molecules prevalent in airway fluid. Furthermore, as a matter-of-fact, it has been observed that bundles of DNA or F-actin formed after addition of histone H1 or lysozyme are efficiently dissolved by soluble multivalent anions such as polymeric aspartate or glutamate. Addition of poly-aspartate or poly-glutamate also disperses DNA and actin-containing bundles in CF sputum and lowers the elastic moduli of these samples to levels comparable to those obtained after treatment with DNase I or gelsolin. Addition of

02 May 2016

2012212269

poly-aspartic acid also increased DNase activity when added to samples containing DNA bundles formed with histone H1. When added to CF sputum, poly-aspartic acid significantly reduced the growth of bacteria, suggesting activation of endogenous antibacterial factors. These findings suggest that soluble multivalent anions have potential alone or in combination with other mucolytic agents to selectively dissociate the large bundles of charged biopolymers that form in CF sputum.

Hence, NAC, unfractionated heparin, reduced glutathione, dithiols, Trx, DHLA, other monothiol, DNase, dornase alfa, hypertonic formulations (*e.g.*, osmolalities greater than about 350 mOsmol/kg), multivalent anions such as polymeric aspartate or glutamate, glycosidases and other examples listed above can be combined with pirfenidone or pyridone analog compounds and other mucolytic agents for aerosol administration to improve antifibrotic and/or antiinflammatory activity through better distribution from reduced sputum viscosity, and improved clinical outcome through improved pulmonary function (from improved sputum mobility and mucociliary clearance) and decreased lung tissue damage from the immune inflammatory response.

Characterization of Inhalation Devices

The efficiency of a particular inhalation device can be measured by many different ways, including an analysis of pharmacokinetic properties, measurement of lung deposition percentage, measurement of respirable delivery dose (RDD), a determination of output rates, geometric standard deviation values (GSD), and mass median aerodynamic diameter values (MMAD) among others.

Methods and systems for examining a particular inhalation device are known. One such system consists of a computer means and a hollow cylinder in a pump means with a connecting piece to which an inhalation device is to be connected. In the pump means there is a piston rod, which extends out of the hollow cylinder. A linear drive unit can be activated in such a manner that one or more breathing pattern will be simulated on the connecting piece of the pump means. In order to be able to carry out the evaluation of the inhalation device, the computer is connected in an advantageous configuration with a data transmission means. With the aid of the data transmission means, the computer can be connected with another computer with specific data banks, in order to exchange the data of breathing patterns. In this manner, a breathing pattern library which is as representative as possible can be very rapidly

02 May 2016
2012212269

formed. U.S. Pat. No. 6,106,479 discloses this method for examining an inhalation device in more detail, and is hereby incorporated by reference in its entirety.

Pharmacokinetic Profile

Pharmacokinetics is concerned with the uptake, distribution, metabolism and excretion of a drug substance. A pharmacokinetic profile comprises one or more biological measurements designed to measure the absorption, distribution, metabolism and excretion of a drug substance. One way of visualizing a pharmacokinetic profile is by means of a blood plasma concentration curve, which is a graph depicting mean active ingredient blood plasma concentration on the Y-axis and time (usually in hours) on the X-axis. Some pharmacokinetic parameters that may be visualized by means of a blood plasma concentration curve include:

- C_{max}: The maximum plasma concentration in a patient.
- AUC: area under the curve
- TOE: time of exposure
- T_{1/2}: period of time it takes for the amount in a patient of drug to decrease by half
- T_{max}: The time to reach maximum plasma concentration in a patient

Pharmacokinetics (PK) is concerned with the time course of a therapeutic agent, such as pirfenidone, or a pyridone analog compound concentration in the body.

Pharmacodynamics (PD) is concerned with the relationship between pharmacokinetics and efficacy *in vivo*. PK/PD parameters correlate the therapeutic agent, such as exposure with efficacious activity. Accordingly, to predict the therapeutic efficacy of a therapeutic agent, such as with diverse mechanisms of action different PK/PD parameters may be used.

Any standard pharmacokinetic protocol can be used to determine blood plasma concentration profile in humans following administration of a formulation comprising pirfenidone or a pyridone analog compound described herein, and thereby establish whether that formulation meets the pharmacokinetic criteria set out herein. For example, but in no way limiting, a type of a randomized single-dose crossover study can be utilized using a group of healthy adult human subjects. The number of subjects can be sufficient to provide adequate control of variation in a statistical analysis, and is typically about 8 or greater, although in certain embodiments a smaller group can be used. In one embodiment, a subject receives administration, at time zero, a single dose of a test inhalation mixture comprising

02 May 2016
2012212269

pirfenidone or a pyridone analog compound. Blood samples are collected from each subject prior to administration and at several intervals after administration. Plasma can be separated from the blood samples by centrifugation and the separated plasma is analyzed, for example, by a validated high performance liquid chromatography/tandem weight spectrometry (LC/APCI-MS/MS) procedure such as, for example, those described in Ramu et al., *Journal of Chromatography B*, 751:49–59 (2001). In other embodiments, data from a single subject may be collected and may be used to construct a pK profile and may be indicative of an enhanced pharmacokinetic profile. In still other embodiments, appropriate in vitro models may be used to construct a pK profile and may be demonstrate or indicate an enhanced pharmacokinetic profile.

In some embodiments, a human pK profile can be may be obtained by the use of allometric scaling. In one embodiment, rat aerosol lung data and plasma delivery is scaled to provide an indication of possible humans data. In one embodiment, allometric scaling uses parameters established in the US FDA Guidance for Industry - Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers.

Any aqueous inhalable mixture giving the desired pharmacokinetic profile may be suitable for administration according to the present methods.

As used herein, the “peak period” of a pharmaceutical’s *in vivo* concentration is defined as that time of the pharmaceutical dosing interval when the pharmaceutical concentration is not less than 50% of its maximum plasma or site-of-disease concentration. In some embodiments, “peak period” is used to describe an interval of pirfenidone or a pyridone analog compound dosing.

In some embodiments, when considering treatment of lung diseases, a method or system described herein provides at least a two-fold enhancement in pharmacokinetic profile for treatment of the lung disease. In some embodiments, the methods and systems described herein provide at least a two-fold enhancement in the lung tissue pharmacokinetic profile of pirfenidone or pyridone analog compound as compared to oral administration.

In some embodiments, a delayed appearance of 5-carboxy-pirfenidone (the primary pirfenidone liver metabolite) has been observed from the methods and systems described herein. In some embodiments, rapid elimination of pirfenidone from the lung tissue has been observed. Comparing the initial rapid elimination of pirfenidone from the lung tissue and

02 May 2016
2012212269

parallel appearance of pirfenidone in the plasma suggest that direct pulmonary administration may be a good route for systemic administration of pirfenidone. The delayed appearance of 5-carboxy-pirfenidone metabolite supports this hypothesis in that this metabolite serves as a marker for re-circulation of pirfenidone to the lung and other tissues following direct aerosol administration to the lung. In some embodiments, re-circulated pirfenidone is likely important to support long-term, elevated pirfenidone levels in the lung and other tissues of potential efficacy.

In some embodiments, the amount of pirfenidone or pyridone analog compound that is administered to a human by inhalation may be calculated by measuring the amount of pirfenidone or pyridone analog compound and associated metabolites that are found in the urine. In some embodiments, about 80% of administered pirfenidone is excreted in the urine (with 95% being the primary metabolite, 5-carboxy-pirfenidone). In some embodiments, the calculation based on compound and metabolites in urine may be done through a 48 urine collection (following a single administration), whereby the total amount of pirfenidone or pyridone analog compound delivered to the human is the sum of measured pirfenidone and its metabolites. By non-limiting example, knowing that 80% of pirfenidone is excreted, a 50 mg sum urinary measurement of pirfenidone and its metabolites would translate to a delivered dose of about 63 mg (50 mg divided by 80%). If by non-limiting example the inhaled aerosol fine-particle fraction (FPF) is 75%, one may assume that about 75% of the drug deposited in the lung (and about 25% was swallowed, and subsequently absorbed from the gut with 80% excreted in the urine). Integrating these two calculations, of a 63 mg delivered dose (as measured by urinary excretion), about 47 mg would be the amount of inhaled aerosol pirfenidone delivered to the lung (the actual RDD; calculated as the product of 63 mg and a 75% FPF). This RDD can then be used in a variety of calculations, including lung tissue concentration.

In some embodiments, method or systems described herein provide pharmacokinetic profiles of pirfenidone or pyridone analog compounds as described herein. In some embodiments, method or systems described herein provide pharmacokinetic profiles of pirfenidone or pyridone analog compounds as in Examples 6 and 7.

2012212269 02 May 2016

Examples**Example 1: Pirfenidone Formulations**

Non-limiting examples of compositions of pirfenidone include those described in Table 1-1 through Table 1-11.

Table 1-1

Composition no.	Ingredient and Amount						
	Pirfenidone	Phosphate Buffer (sodium salt), pH 6.2 (mM)	Phosphate Buffer (sodium salt), pH 7.3 (mM)	Citrate Buffer (acid/sodium salt), pH 5.8 (mM)	Sodium Chloride (μmols)	Magnesium Chloride (μmols)	Water
1	1 mg to 500 mg (5 μmols to 3 mmols)	-	-	0.01 mM to 500 mM	-	-	q.s. to 5 mL
2	1 mg to 500 mg (5 μmols to 3 mmols)	0.01 mM to 500 mM	-	-	-	-	q.s. to 5 mL
3	1 mg to 500 mg (5 μmols to 3 mmols)	-	0.01 mM to 500 mM	-	-	-	q.s. to 5 mL
4	54 μmols	0.01 to 500	-	-	150	-	q.s. to 5 mL
5	54 μmols	-	0.01 to 500	-	150	-	q.s. to 5 mL
6	54 μmols	-	-	0.01 to 500	150	-	q.s. to 5 mL
7	54 μmols	0.01 to 500	-	-	-	150	q.s. to 5 mL
8	54 μmols	-	0.01 to 500	-	-	150	q.s. to 5 mL
9	54 μmols	-	-	0.01 to 500	-	150	q.s. to 5 mL
10	54 μmols	0.01 to 500	-	-	13.5	-	q.s. to 5 mL
11	54 μmols	-	0.01 to 500	-	13.5	-	q.s. to 5 mL

2012212269 02 May 2016

Composition no.	Ingredient and Amount						
	Pirfenidone	Phosphate Buffer (sodium salt), pH 6.2 (mM)	Phosphate Buffer (sodium salt), pH 7.3 (mM)	Citrate Buffer (acid/sodium salt), pH 5.8 (mM)	Sodium Chloride (μmols)	Magnesium Chloride (μmols)	Water
12	54 μmols	-	-	0.01 to 500	13.5	-	q.s. to 5 mL
13	54 μmols	0.01 to 500	-	-	-	13.5	q.s. to 5 mL
14	54 μmols	-	0.01 to 500	-	-	13.5	q.s. to 5 mL
15	54 μmols	-	-	0.01 to 500	-	13.5	q.s. to 5 mL
16	54 μmols	0.01 to 500	-	-	54	-	q.s. to 5 mL
17	54 μmols	-	0.01 to 500	-	54	-	q.s. to 5 mL
18	54 μmols	-	-	0.01 to 500	54	-	q.s. to 5 mL
19	54 μmols	0.01 to 500	-	-	-	54 μmols	q.s. to 5 mL
20	54 μmols	-	0.01 to 500	-	-	54 μmols	q.s. to 5 mL
21	54 μmols	-	-	0.01 to 500	-	54 μmols	q.s. to 5 mL
22	54 μmols	0.01 to 500	-	-	27	-	q.s. to 5 mL
23	54 μmols	-	0.01 to 500	-	27	-	q.s. to 5 mL
24	54 μmols	-	-	0.01 to 500	27	-	q.s. to 5 mL
25	54 μmols	0.01 to 500	-	-	-	27	q.s. to 5 mL
26	54 μmols	-	0.01 to 500	-	-	27	q.s. to 5 mL
27	54 μmols	-	-	0.01 to 500	-	27	q.s. to 5 mL

2012212269 02 May 2016

Table 1-2

Composition no.	Ingredient and Amount						
	Pirfenidone	Citrate Buffer (acid/sodium salt), pH 2.0 to 9.0 (mM)	Phosphate Buffer (monobasic/dibasic sodium salts), pH 2.0 to 9.0 (mM)	Sodium Chloride (μ moles)	Magnesium Chloride	Saccharin (sodium salt) (mM)	Water
28	5 μ moles to 3 mmols	0.01 to 500	-	-	1 μ mol to 15 mmols	0.01 to 10.0	q.s. to 5 mL
29	5 μ moles to 3 mmols	-	0.01 to 500	-	1 μ mol to 15 mmols	0.01 to 10.0	q.s. to 5 mL
30	5 μ moles to 3 mmols	0.01 to 500	-	1 μ mol to 15 mmols	-	0.01 to 10.0	q.s. to 5 mL
31	5 μ moles to 3 mmols	-	0.01 to 500	1 μ mol to 15 mmols	-	0.01 to 10.0	q.s. to 5 mL

Table 1-3

Composition no.	Ingredient and Amount					
	Pirfenidone	Citrate Buffer (acid/sodium salt), pH 5.8 (mM)	Phosphate Buffer (monobasic/dibasic sodium salts), pH 6.2 (mM)	Phosphate Buffer (monobasic/dibasic sodium salts), pH 7.3 (mM)	Saccharin (sodium salt) (mM)	Water
32	1 mg to 500 mg (5 μ moles to 3 mmols)	0.01 to 500	-	-	0.01 to 10.0	q.s. to 5 mL
33	1 mg to 500 mg (5 μ moles to 3 mmols)	-	0.01 to 500	-	0.01 to 10.0	q.s. to 5 mL
34	1 mg to 500 mg (5 μ moles to 3 mmols)			0.01 to 500	0.01 to 10.0	q.s. to 5 mL

02 May 2016

2012212269

In some embodiments, pirfenidone exhibited aqueous solubility to ~17 mg/mL across a pH range of about 4.0 to about 8.0. However, at this (and lower) concentration it was determined that salt addition was required to improve acute tolerability upon inhalation of a nebulized solution (otherwise a hypotonic solution). To address tonicity, NaCl or MgCl₂ were added. In some embodiments, addition of NaCl improved acute tolerability, but destabilized the formulation and resulted in precipitation upon ambient storage. In some embodiments, it was determined that addition of MgCl₂ maintained a stable, soluble solution at this concentration with an osmolality in a tolerable range. By non-limiting example, 81 mM MgCl₂ provides a 1:1 mole ratio of magnesium to pirfenidone where pirfenidone is at 15 mg/mL (or 81 mM). This effect was also observed at various pirfenidone concentrations with 1:1 and 1:2 mole ratios of magnesium to pirfenidone, but not at ratios less than or equal to 0.25:1 or greater than or equal to 1:0.33 magnesium to pirfenidone, respectively. This effect was observed in 5 mM to 50 mM citrate buffer at pH 4.0 and pH 5.8, and 5 mM to 50 mM phosphate buffer at pH 6.2, pH 7.3 and pH 7.8. Other observations included: 1) Formulations of both buffer systems exhibited a metallic, bitter flavor and throat irritation; 2) From 0.1 to 0.7 mM sodium saccharin was required to taste mask these formulations; 3) 0.6 mM sodium saccharin was the best concentration and improved the flavor of 2:1 mol ratio pirfenidone to magnesium in phosphate buffer more so than the 1:1 mol ratio; 4) The taste of 2:1 mol ratio pirfenidone to magnesium in citrate buffer without sodium saccharin was equivalent to the 1:1 mol ratio pirfenidone to magnesium in phosphate buffer with 0.6 mM sodium saccharin; 5) The taste of 2:1 mol ratio pirfenidone to magnesium in citrate buffer with 0.2 mM sodium saccharin was equivalent to the 2:1 mol ratio pirfenidone to magnesium in phosphate buffer with 0.6 mM sodium saccharin; 6) The taste of 1:1 mol ratio pirfenidone to magnesium in citrate buffer with 0.6 mM sodium saccharin was equivalent to 2:1 mol ratio pirfenidone to magnesium in phosphate buffer 0.6 mM sodium saccharin; and 7) 1:1 mol ratio pirfenidone to magnesium dissolved in up to 40% the time required to dissolve 2:1 mol ratio pirfenidone to magnesium in either buffer system at ~pH 6. This effect was not observed at ~pH 8.

30

2012212269 02 May 2016

Table 1-4

Composition no.	Ingredient and Amount								
	Pirfenidone (mg)	Phosphate Buffer (monobasic/dibasic sodium salts), pH 5.5 to 8.5 (mM)	Ethanol (% v/v)	Propylene Glycol (% v/v)	Glycerol (% v/v)	Polysorbate 80 (% v/v)	Cetylpyridinium Bromide (or chloride) (%)	Osmolality (mOsmo/kg)	Water
35	1 to 500	0.01 to 500	0.001 to 25	-	-	-	-	50 to 5000	q.s. to 5 mL
36*	1 to 500	0.01 to 500	-	0.001 to 25	-	-	-	50 to 5000	q.s. to 5 mL
37	1 to 500	0.01 to 500	-	-	0.001 to 25	-	-	50 to 5000	q.s. to 5 mL
38	1 to 500	0.01 to 500	-	-	-	0.0001 to 1.0	-	50 to 5000	q.s. to 5 mL
39 *	1 to 500	0.01 to 500	-	-	-	-	0.0001 to 5.0	50 to 5000	q.s. to 5 mL
40	1 to 500	0.01 to 500	0.001 to 25	0.001 to 25	-	-	-	50 to 5000	q.s. to 5 mL
41	1 to 500	0.01 to 500	0.001 to 25	-	0.001 to 25	-	-	50 to 5000	q.s. to 5 mL
42	1 to 500	0.01 to 500	0.001 to 25	-	-	0.0001 to 1.0	-	50 to 5000	q.s. to 5 mL
43	1 to 500	0.01 to 500	0.001 to 25	-	-	-	0.0001 to 5.0	50 to 5000	q.s. to 5 mL
44	1 to 500	0.01 to 500	0.001 to 25	0.001 to 25	0.001 to 25	-	-	50 to 5000	q.s. to 5 mL
45	1 to 500	0.01 to 500	0.001 to 25	0.001 to 25	-	0.0001 to 1.0	-	50 to 5000	q.s. to 5 mL
46	1 to 500	0.01 to 500	0.001 to 25	0.001 to 25	-	-	0.0001 to 5.0	50 to 5000	q.s. to 5 mL
47	1 to 500	0.01 to 500	0.001 to 25	0.001 to 25	0.001 to 25	0.0001 to 1.0	-	50 to 5000	q.s. to 5 mL
48	1 to 500	0.01 to 500	0.001 to 25	0.001 to 25	-	0.0001 to 1.0	-	50 to 5000	q.s. to 5 mL
49	1 to 500	0.01 to 500	0.001 to 25	0.001 to 25	0.001 to 25	-	0.0001 to 5.0	50 to 5000	q.s. to 5 mL
50	1 to 500	0.01 to 500	0.001 to 25	0.001 to 25	-	-	0.0001 to 5.0	50 to 5000	q.s. to 5 mL

* Phosphate Buffer (monobasic/dibasic sodium salts), pH 6.2

2012212269 02 May 2016

Table 1-5

Composition no.	Ingredient and Amount								
	Pirfenidone (mg)	Citrate Buffer (citric acid/sodium citrate), pH 3.5 to pH 6.5	Ethanol (% v/v)	Propylene Glycol (% v/v)	Glycerol (% v/v)	Polysorbate 80 (% v/v)	Cetylpyridinium Bromide (or chloride) (%)	Osmolality (mOsmo/kg)	Water
51	1 to 500	0.01 to 500	0.001 to 25	-	-	-	-	50 to 5000	q.s. to 5 mL
52	1 to 500	0.01 to 500	-	0.001 to 25	-	-	-	50 to 5000	q.s. to 5 mL
53	1 to 500	0.01 to 500	-	-	0.001 to 25	-	-	50 to 5000	q.s. to 5 mL
54	1 to 500	0.01 to 500	-	-	-	0.0001 to 1.0	-	50 to 5000	q.s. to 5 mL
55	1 to 500	0.01 to 500	-	-	-	-	0.0001 to 5.0	50 to 5000	q.s. to 5 mL
56	1 to 500	0.01 to 500	0.001 to 25	0.001 to 25	-	-	-	50 to 5000	q.s. to 5 mL
57	1 to 500	0.01 to 500	0.001 to 25	-	0.001 to 25	-	-	50 to 5000	q.s. to 5 mL
58	1 to 500	0.01 to 500	0.001 to 25	-	-	0.0001 to 1.0	-	50 to 5000	q.s. to 5 mL
59	1 to 500	0.01 to 500	0.001 to 25	-	-	-	0.0001 to 5.0	50 to 5000	q.s. to 5 mL
60	1 to 500	0.01 to 500	0.001 to 25	0.001 to 25	0.001 to 25	-	-	50 to 5000	q.s. to 5 mL
61	1 to 500	0.01 to 500	0.001 to 25	0.001 to 25	-	0.0001 to 1.0	-	50 to 5000	q.s. to 5 mL
62	1 to 500	0.01 to 500	0.001 to 25	0.001 to 25	-	-	0.0001 to 5.0	50 to 5000	q.s. to 5 mL
63	1 to 500	0.01 to 500	0.001 to 25	0.001 to 25	0.001 to 25	0.0001 to 1.0	-	50 to 5000	q.s. to 5 mL
64	1 to 500	0.01 to 500	0.001 to 25	0.001 to 25	-	0.0001 to 1.0	-	50 to 5000	q.s. to 5 mL
65	1 to 500	0.01 to 500	0.001 to 25	0.001 to 25	0.001 to 25	-	0.0001 to 5.0	50 to 5000	q.s. to 5 mL
66	1 to 500	0.01 to 500	0.001 to 25	0.001 to 25	-	-	0.0001 to 5.0	50 to 5000	q.s. to 5 mL

2012212269 02 May 2016

Table 1-6

Composition no.	Ingredient and Amount									
	Pirfenidone (mg)	Phosphate Buffer (monobasic/dibasic sodium salts), pH 5.5 to 8.5 (mM)	Ethanol (% v/v)	Propylene Glycol (% v/v)	Glycerol (% v/v)	Polysorbate 80 (%)	Cetylpyridinium Bromide (or chloride) (%)	Chloride ion (sodium, magnesium or calcium salts) (%)	Osmolality (mOsmo/kg)	Water
67	1 to 500	0.01 to 500	0.001 to 25	-	-	-	-	0.01 to 5	50 to 5000	q.s. to 5 mL
68*	1 to 500	0.01 to 500	-	0.001 to 25	-	-	-	0.01 to 5	50 to 5000	q.s. to 5 mL
69	1 to 500	0.01 to 500	-	-	0.001 to 25	-	-	0.01 to 5	50 to 5000	q.s. to 5 mL
70	1 to 500	0.01 to 500	-	-	-	0.0001 to 1.0	-	0.01 to 5	50 to 5000	q.s. to 5 mL
71 *	1 to 500	0.01 to 500	-	-	-	-	0.0001 to 5.0	0.01 to 5	50 to 5000	q.s. to 5 mL
72	1 to 500	0.01 to 500	0.001 to 25	0.001 to 25	-	-	-	0.01 to 5	50 to 5000	q.s. to 5 mL
73	1 to 500	0.01 to 500	0.001 to 25	-	0.001 to 25	-	-	0.01 to 5	50 to 5000	q.s. to 5 mL
74	1 to 500	0.01 to 500	0.001 to 25	-	-	0.0001 to 1.0	-	0.01 to 5	50 to 5000	q.s. to 5 mL
75	1 to 500	0.01 to 500	0.001 to 25	-	-	-	0.0001 to 5.0	0.01 to 5	50 to 5000	q.s. to 5 mL
76	1 to 500	0.01 to 500	0.001 to 25	0.001 to 25	0.001 to 25	-	-	0.01 to 5	50 to 5000	q.s. to 5 mL
77	1 to 500	0.01 to 500	0.001 to 25	0.001 to 25	-	0.0001 to 1.0	-	0.01 to 5	50 to 5000	q.s. to 5 mL
78	1 to	0.01 to	0.001	0.001	-	-	0.0001	0.01 to	50 to	q.s.

2012212269 02 May 2016

Composition no.	Ingredient and Amount									
	Pirfenidone (mg)	Phosphate Buffer (monobasic/dibasic sodium salts), pH 5.5 to 8.5 (mM)	Ethanol (% v/v)	Propylene Glycol (% v/v)	Glycerol (% v/v)	Polysorbate 80 (%)	Cetylpyridinium Bromide (or chloride) (%)	Chloride ion (sodium, magnesium or calcium salts) (%)	Osmolality (mOsmo/kg)	Water
	500	500	to 25	to 25			to 5.0	5	5000	to 5 mL
79	1 to 500	0.01 to 500	0.001 to 25	0.001 to 25	0.001 to 25	0.0001 to 1.0	-	0.01 to 5	50 to 5000	q.s. to 5 mL
80	1 to 500	0.01 to 500	0.001 to 25	0.001 to 25	-	0.0001 to 1.0	-	0.01 to 5	50 to 5000	q.s. to 5 mL
81	1 to 500	0.01 to 500	0.001 to 25	0.001 to 25	0.001 to 25	-	0.0001 to 5.0	0.01 to 5	50 to 5000	q.s. to 5 mL
82	1 to 500	0.01 to 500	0.001 to 25	0.001 to 25	-	-	0.0001 to 5.0	0.01 to 5	50 to 5000	q.s. to 5 mL

* Phosphate Buffer (monobasic/dibasic sodium salts), pH 6.2

2012212269 02 May 2016

Table 1-7

Composition no.	Ingredient and Amount									
	Pirfenidone (mg)	Citrate Buffer (citric acid/sodium citrate), pH 3.5 to pH 6.5 (mM)	Ethanol (% v/v)	Propylene Glycol (% v/v)	Glycerol (% v/v)	Polysorbate 80 (%)	Cetylpyridinium Bromide (or chloride) (%)	Chloride ion (sodium, magnesium or calcium salts) (%)	Osmolality (mOsmo/kg)	Water
83	1 to 500	0.01 to 500	0.001 to 25	-	-	-	-	0.01 to 5	50 to 5000	q.s. to 5 mL
84	1 to 500	0.01 to 500	-	0.001 to 25	-	-	-	0.01 to 5	50 to 5000	q.s. to 5 mL
85	1 to 500	0.01 to 500	-	-	0.001 to 25	-	-	0.01 to 5	50 to 5000	q.s. to 5 mL
86	1 to 500	0.01 to 500	-	-	-	0.0001 to 1.0	-	0.01% to 5%	50 to 5000	q.s. to 5 mL
87	1 to 500	0.01 to 500	-	-	-	-	0.0001 to 5.0	0.01 to 5	50 to 5000	q.s. to 5 mL
88	1 to 500	0.01 to 500	0.001 to 25	0.001 to 25	-	-	-	0.01 to 5	50 to 5000	q.s. to 5 mL
89	1 to 500	0.01 to 500	0.001 to 25	-	0.001 to 25	-	-	0.01 to 5	50 to 5000	q.s. to 5 mL
90	1 to 500	0.01 to 500	0.001 to 25	-	-	0.0001 to 1.0	-	0.01 to 5	50 to 5000	q.s. to 5 mL
91	1 to 500	0.01 to 500	0.001 to 25	-	-	-	0.0001 to 5.0	0.01 to 5	50 to 5000	q.s. to 5 mL
92	1 to 500	0.01 to 500	0.001 to 25	0.001 to 25	0.001 to 25	-	-	0.01 to 5	50 to 5000	q.s. to 5 mL
93	1 to 500	0.01 to 500	0.001 to 25	0.001 to 25	-	0.0001 to 1.0	-	0.01 to 5	50 to 5000	q.s. to 5 mL

2012212269 02 May 2016

Composition no.	Ingredient and Amount									
	Pirfenidone (mg)	Citrate Buffer (citric acid/sodium citrate), pH 3.5 to pH 6.5 (mM)	Ethanol (% v/v)	Propylene Glycol (% v/v)	Glycerol (% v/v)	Polysorbate 80 (%)	Cetylpyridinium Bromide (or chloride) (%)	Chloride ion (sodium, magnesium or calcium salts) (%)	Osmolality (mOsmo/kg)	Water
94	1 to 500	0.01 to 500	0.001 to 25	0.001 to 25	-	-	0.0001 to 5.0	0.01 to 5	50 to 5000	q.s. to 5 mL
95	1 to 500	0.01 to 500	0.001 to 25	0.001 to 25	0.001 to 25	0.0001 to 1.0	-	0.01 to 5	50 to 5000	q.s. to 5 mL
96	1 to 500	0.01 to 500	0.001 to 25	0.001 to 25	-	0.0001 to 1.0	-	0.01 to 5	50 to 5000	q.s. to 5 mL
97	1 to 500	0.01 to 500	0.001 to 25	0.001 to 25	0.001 to 25	-	0.0001 to 5.0	0.01 to 5	50 to 5000	q.s. to 5 mL
98	1 to 500	0.01 to 500	0.001 to 25	0.001 to 25	-	-	0.0001 to 5.0	0.01 to 5	50 to 5000	q.s. to 5 mL

5

10

2012212269 02 May 2016

Table 1-8

Composition no.	Ingredient and Amount					
	Pirfenidone (mg)	Citrate Buffer (citric acid/sodium citrate), pH 4.0 to pH 5.0 (mM)	Ethanol (% v/v/)	Propylene Glycol (% v/v)	Osmolality (mOsmo/kg)	Water
99	5 mg (27 μ moles)	5	0.5%	1.0%	200 to 400	q.s. to 5 mL
100	5 mg (27 μ moles)	5	1.0%	2.0%	400 to 600	q.s. to 5 mL
101	10 mg (54 μ moles)	5	1.0%	2.0%	400 to 600	q.s. to 5 mL
102	15 (81 μ moles)	5	1.0%	2.0%	400 to 600	q.s. to 5 mL
103	25 mg (135 μ moles)	5	1.0%	2.0%	400 to 600	q.s. to 5 mL
104	37.5 mg (202 μ moles)	5	1.0%	2.0%	400 to 600	q.s. to 5 mL
105	75 mg (405 μ moles)	5	1.0%	2.0%	400 to 600	q.s. to 5 mL
106	100 mg (541 μ moles)	5	2.0%	4.0%	900 to 1100	q.s. to 5 mL
107	115 mg (621 μ moles)	5	4.0%	8.0%	1800 to 2100	q.s. to 5 mL
108	150 mg (810 μ moles)	5	6.0%	12.0%	1800 to 2100	q.s. to 5 mL
109	190 mg (1027 μ moles)	5	8.0%	16.0%	3500 to 3900	q.s. to 5 mL
110	220 mg (1189 μ moles)	5	8.0%	16.0%	3600 to 4000	q.s. to 5 mL

2012212269 02 May 2016

Table 1-9

Composition no.	Ingredient and Amount					
	Pirfenidone (mg)	Phosphate Buffer (monobasic/di basic sodium salts), pH 6.0 to pH 7.0	Ethanol (% v/v)	Propylene Glycol (% v/v)	Osmolality (mOsmo/kg)	Water
111	5 mg (27 μ mol)	5	0.5%	1.0%	200 to 400	q.s. to 5 mL
112	5 mg (27 μ mol)	5	1.0%	2.0%	200 to 600	q.s. to 5 mL
113	10 mg (54 μ mol)	5	1.0%	2.0%	400 to 600	q.s. to 5 mL
114	15 (81 μ mol)	5	1.0%	2.0%	400 to 600	q.s. to 5 mL
115	25 mg (135 μ mol)	5	1.0%	2.0%	400 to 600	q.s. to 5 mL
116	37.5 mg (202 μ mol)	5	1.0%	2.0%	400 to 600	q.s. to 5 mL
117	75 mg (405 μ mol)	5	1.0%	2.0%	400 to 600	q.s. to 5 mL
118	100 mg (541 μ mol)	5	2.0%	4.0%	900 to 1100	q.s. to 5 mL
119	115 mg (621 μ mol)	5	4.0%	8.0%	1800 to 2100	q.s. to 5 mL
120	150 mg (810 μ mol)	5	6.0%	12.0%	1800 to 2100	q.s. to 5 mL
121	190 mg (1027 μ mol)	5	8.0%	16.0%	3500 to 3900	q.s. to 5 mL
122	220 mg (1189 μ mol)	5	8.0%	16.0%	3600 to 4000	q.s. to 5 mL

2012212269 02 May 2016

Table 1-10

Composition no.	Ingredient and Amount						
	Pirfenidone (mg)	Citrate Buffer (citric acid/sodium citrate), pH 4.0 to pH 5.0 (mM)	Ethanol (% v/v)	Propylene Glycol (% v/v)	Chloride ion (sodium, magnesium or calcium salts)	Osmolality (mOsmo/kg)	Water
123	5 mg (27 μmols)	5	0.5%	1.0%	0.1% to 0.9%	200 to 500	q.s. to 5 mL
124	5 mg (27 μmols)	5	1.0%	2.0%	0.1% to 0.9%	400 to 700	q.s. to 5 mL
125	10 mg (54 μmols)	5	1.0%	2.0%	0.1% to 0.9%	400 to 700	q.s. to 5 mL
126	15 (81 μmols)	5	1.0%	2.0%	0.1% to 0.9%	400 to 700	q.s. to 5 mL
127	25 mg (135 μmols)	5	1.0%	2.0%	0.1% to 0.9%	400 to 700	q.s. to 5 mL
128	37.5 mg (202 μmols)	5	1.0%	2.0%	0.1% to 0.9%	400 to 700	q.s. to 5 mL
129	75 mg (405 μmols)	5	1.0%	2.0%	0.1% to 0.9%	400 to 700	q.s. to 5 mL
130	100 mg (541 μmols)	5	2.0%	4.0%	0.1% to 0.9%	900 to 1200	q.s. to 5 mL
131	115 mg (621 μmols)	5	4.0%	8.0%	0.1% to 0.9%	1800 to 2200	q.s. to 5 mL
132	150 mg (810 μmols)	5	6.0%	12.0%	0.1% to 0.9%	1800 to 2200	q.s. to 5 mL
133	190 mg (1027 μmols)	5	8.0%	16.0%	0.1% to 0.9%	3500 to 4000	q.s. to 5 mL
134	220 mg (1189 μmols)	5	8.0%	16.0%	0.1% to 0.9%	3600 to 4100	q.s. to 5 mL

2012212269 02 May 2016

Table 1-11

Composition no.	Ingredient and Amount						
	Pirfenidone (mg)	Phosphate Buffer (monobasic/dibasic sodium salts), pH 6.0 to pH 7.0 (mM)	Ethanol	Propylene Glycol	Chloride ion (sodium, magnesium or calcium salts)	Osmolality (mOsmo/kg)	Water
135	5 mg (27 μmols)	5	0.5%	1.0%	0.1% to 0.9%	200 to 500	q.s. to 5 mL
136	5 mg (27 μmols)	5	1.0%	2.0%	0.1% to 0.9%	200 to 700	q.s. to 5 mL
137	10 mg (54 μmols)	5	1.0%	2.0%	0.1% to 0.9%	400 to 700	q.s. to 5 mL
138	15 (81 μmols)	5	1.0%	2.0%	0.1% to 0.9%	400 to 700	q.s. to 5 mL
139	25 mg (135 μmols)	5	1.0%	2.0%	0.1% to 0.9%	400 to 700	q.s. to 5 mL
140	37.5 mg (202 μmols)	5	1.0%	2.0%	0.1% to 0.9%	400 to 700	q.s. to 5 mL
141	75 mg (405 μmols)	5	1.0%	2.0%	-	400 to 700	q.s. to 5 mL
142	100 mg (541 μmols)	5	2.0%	4.0%	0.1% to 0.9%	900 to 1200	q.s. to 5 mL
143	115 mg (621 μmols)	5	4.0%	8.0%	0.1% to 0.9%	1800 to 2200	q.s. to 5 mL
144	150 mg (810 μmols)	5	6.0%	12.0 %	0.1% to 0.9%	1800 to 2200	q.s. to 5 mL
145	190 mg (1027 μmols)	5	8.0%	16.0 %	0.1% to 0.9%	3500 to 4000	q.s. to 5 mL
146	220 mg (1189 μmols)	5	8.0%	16.0 %	0.1% to 0.9%	3600 to 4100	q.s. to 5 mL

Example 2: Buffer and pH Effects Development Study

Pirfenidone solubility in citrate and phosphate buffers were investigated (Table 2). Pirfenidone (250 mg) was reconstituted with 5 mL of buffer in water or water alone and mixed thoroughly with sonication and vortexing. The sample was agitated at ambient temperature overnight. The sample was visually inspected, appearance recorded, centrifuged to sediment any un-dissolved material, and the supernatant withdrawn via syringe through a 0.22 µm PVDF filter. The filtered sample was tested with respect to: appearance, pH (USP <791>), osmolality (USP <785>), and Pirfenidone concentration and Pirfenidone % purity by RP-HPLC. The remaining filtered sample was split into three equal volumes in glass vials and placed at 25°C/60RH, 40°C/75RH and refrigeration. Samples were wrapped in aluminum foil to reduce light exposure. After the first night of incubation, samples were briefly visually inspected for any signs of discoloration or precipitate formation.

Table 2. Buffer/pH Effects Study Results

Buffer	Buffer(mM)	pH	Pirfenidone Saturation Solubility (mg/mL)
Citrate	5	4	18.4
Citrate	50	4	18.1
Citrate	5	6	18.4
Citrate	50	6	16.4
Phosphate	5	6	18.3
Phosphate	50	6	17.2
Phosphate	5	7.5	19.0
Phosphate	50	7.5	16.3
Water	0	7.9	18.4

Table 2 shows the observed solubility of pirfenidone under the conditions described.

Example 3: Co-Solvent and Surfactant Effects

Pirfenidone solubility in the presence of added co-solvent (ethanol, propylene glycol, or glycerin) and surfactant (polysorbate 80 or cetylpyridinium bromide) were investigated. The buffer type, strength, and pH of the aqueous vehicle are selected based on results from the Buffer/pH Effects study results (Example 2). Pirfenidone (375 mg) is reconstituted with 5 mL of each solvent system shown in Table 3.

Table 3. Co-Solvent/Surfactant Effects Study Results

2012212269 02 May 2016

Added Co-Solvent and/or Surfactant, %					% Water	% Citrate Buffer (10 mM)	% Phosphate Buffer (5 mM)	pH	Pirfenidone Saturation Solubility (mg/mL)
EtO H	PG	Gl y	PS80	CP B					
0	0	0	0.04	0	100.0	0	0	6.5	19.9
0	0	0	0	0.1	99.9	0	0	6.2	20.0
0	0	0	0.04	0	100.0	0	0	4.8	8.3
0	0	0	0	0.1	99.9	0	0	4.6	19.3
0	0	0	0.04	0	0	100.0	0	4.5	19.1
0	0	0	0	0.1	0	99.9	0	4.5	19.3
4	0	0	0	0	96.0	0	0	6.9	24.3
0	8	0	0	0	92.0	0	0	6.8	24.6
0	0	4	0	0	96.0	0	0	6.7	20.1
4	0	0	0	0	96.0	0	0	5.0	22.8
0	8	0	0	0	92.0	0	0	5.0	24.3
0	0	4	0	0	96.0	0	0	4.8	20.1
4	0	0	0	0	0	96.0	0	4.5	22.3
0	8	0	0	0	0	92.0	0	4.4	23.2
0	0	4	0	0	0	96.0	0	4.4	19.8
4	0	0	0.04	0	96.0	0	0	6.7	24.5
0	8	0	0.04	0	92.0	0	0	6.6	23.2
0	0	4	0.04	0	96.0	0	0	6.5	20.2
4	0	0	0.04	0	96.0	0	0	4.7	22.5
0	8	0	0.04	0	92.0	0	0	4.6	23.4
0	0	4	0.04	0	96.0	0	0	4.9	20.0
4	0	0	0.04	0	0	96.0	0	4.5	21.9
0	8	0	0.04	0	0	92.0	0	4.5	23.2
0	0	4	0.04	0	0	96.0	0	4.4	17.6
4	0	0	0	0.1	95.9	0	0	6.1	23.9
0	8	0	0	0.1	91.9	0	0	6.2	23.4
0	0	4	0	0.1	95.9	0	0	ND	ND
4	0	0	0	0.1	95.9	0	0	4.9	20.2
0	8	0	0	0.1	91.9	0	0	5.0	22.3
0	0	4	0	0.1	95.9	0	0	ND	ND
4	0	0	0	0.1	0	95.9	0	4.5	20.4
0	8	0	0	0.1	0	91.9	0	4.5	21.0
0	0	4	0	0.1	0	95.9	0	ND	ND
4	8	0	0	0	88.0	0	0	6.2	30.0
4	8	0	0.04	0	88.0	0	0	5.8	28.9
4	8	0	0	0	0	0	88.0	6.6	27.2
4	8	0	0.04	0	0	0	88.0	6.6	29.4
6	12	0	0	0	0	0	82.0	7.0	34.7
8	16	0	0	0	0	0	76.0	7.0	43.7
8	0	0	0	0	0	0	92	6.6	26.7
8	4	0	0	0	0	0	88	6.8	30.4
8	8	0	0	0	0	0	84	6.8	35.0
8	12	0	0	0	0	0	80	6.7	37.7

Added Co-Solvent and/or Surfactant, %					% Water	% Citrate Buffer (10 mM)	% Phosphate Buffer (5 mM)	pH	Pirfenidone Saturation Solubility (mg/mL)
EtOH	PG	Gly	PS80	CPB					
8	16	0	0	0	0	0	76	6.8	45.4
6	16	0	0	0	0	0	78	6.9	40.9
4	16	0	0	0	0	0	80	6.9	36.8
2	16	0	0	0	0	0	82	6.8	31.0
0	16	0	0	0	0	0	84	6.8	29.3

* Buffer type, buffer strength, and pH chosen on the basis of Buffer/pH study results (Example 2). EtOH: ethanol, PG: propylene glycol, Gly: glycerol, PS80: polysorbate 80 (Tween 80), CPB: Cetylpyridinium chloride. % in Table 3 refers to volume/volume.

Each sample was agitated at ambient temperature overnight. The samples were visually inspected and appearance recorded. Samples were centrifuged to sediment any undissolved material and the supernatant withdrawn via syringe through a 0.22 µm PVDF filter. The filtered sample was tested with respect to: appearance, pH (USP <791>), osmolality (USP <785>), and Pirfenidone concentration and Pirfenidone % purity by RP-HPLC. The remaining filtered sample was split into three equal volumes in glass vials and placed at 25°C/60RH, 40°C/75RH and refrigeration. Samples are wrapped in aluminum foil to reduce light exposure. After the first night of incubation, samples are briefly visually inspected for any signs of discoloration or precipitate formation.

Both ethanol (EtOH) and propylene glycol (PG) increase the saturation solubility of pirfenidone. Ethanol and propylene glycol together have an additive effect in increasing the saturation solubility of pirfenidone.

Selected formulations were subjected to osmolality determination and nebulization for taste testing and throat irritation and or cough response. Table 4 shows these results.

2012212269 02 May 2016

Table 4. Compositions and Additional Analysis

Added Co-Solvent and/or Surfactant (%) ^a		Sodium Saccharin (mM)	%Phosphate Buffer (5 mM)	pH	Pirfenidone (mg/mL)	Osmolality (mOsmo/Kg)	Taste	Throat Irritation?	Cough Response?
EtOH	PG								
4	8	0	88	6.6	27.2	~1830*	4.5 micron aerosol particle: Mild taste, unremarkable flavor	No	No
6	12	0	82	7.0	34.7	~2750*	4.5 micron aerosol particle: Mild taste, slight sweet flavor, slight bitter after-taste	No	No
8	16	0	76	7.0	43.7	3672	4.5 micron aerosol particle: Mild taste, moderate sweet flavor, moderate bitter after-taste 3.5 micron aerosol particle: Mild taste, similar sweet flavor and bitter after-taste as 6% EtOH + 12% PG	No	No
8	16	0.3	76	7.0	43.7	3672	3.5 micron aerosol particle: Mild taste, similar sweet flavor and slightly bitter after-taste similar to 6% EtOH + 12% PG	No	No
8	16	0	76	4.5	0	3672	3.5 micron aerosol particle: Mild taste, slightly sweeter than 6% EtOH + 12% PG, with similar bitter after-taste	No	No

* Calculated. a - % volume/volume

Results from Table 4 show that co-solvent-containing formulations contain a relatively high osmolality. Unexpectedly, these high osmolar solutions do not exhibit poor inhalation tolerability. Solutions containing up to 8% (v/v) ethanol plus 16% (v/v) propylene glycol are well-tolerated, have a slight sweet flavor with minimal bitter after-taste, minimal throat irritation and minimal stimulation of cough response. Formulations lacking co-solvents

are limited to about 15 mg/mL. These same formulations exhibited a bitter, slightly metallic taste. Unexpectedly, co-solvent-enabling high concentration pirfenidone formulations (by non-limiting example up to 44 mg/mL) do not exhibit these poor taste characteristics.

Saturated pirfenidone formulations appeared stable out to 2-5 days under the tested conditions. However, in all cases pirfenidone eventually re-crystallized. This re-crystallization was not inhibited by pre-filtration of the sample. From this observation, pirfenidone concentrations less than saturation were explored. 85% saturation pirfenidone concentrations were exposed to several temperatures. These results are shown in Table 5.

Table 5. Compositions and Additional Analysis

Added Co-Solvent (%)		%Phosphate Buffer (5 mM)	pH	Pirfenidone (mg/mL)	Recrystallization upon storage ^a			
EtOH	PG				25°C	15°C	4°C	-20°C
4	8	88	6.6	27.2 ^b	Yes	ND ^d	ND	ND
4	8	88	6.6	23.0 ^e	No	No	No	Yes ^f
6	12	82	7.0	34.7	Yes	ND	ND	ND
6	12	82	7.0	29.5	No	No	No	Yes ^f
8	16	76	7.0	43.7	Yes	ND	ND	ND
8	16	76	7.0	37.0	No	No	No	Yes ^f

a. Observation after overnight storage at designated temperature

b. Pirfenidone saturation solubility at given formulation

c. Calculated

d. Not determined

e. Pirfenidone concentration at 85% saturation solubility

f. Crystals re-dissolved at 25°C without agitation

% refers to % v/v

Results from Table 5 show that these 85% pirfenidone saturation formulations do not re-crystallize down to 4°C (at least following overnight incubation). These results suggest that these formulations will survive periodic exposures down to 4°C, and even upon freezing will re-dissolve without agitation.

Additional studies examined pirfenidone stability in 5 mM sodium phosphate buffer, pH 6.5, as a function of optimized co-solvent strength for stability assessment. The target concentrations represent roughly 85% of the saturated concentration possible at each specified co-solvent concentration. Two additional formulations examined pirfenidone stability at 1 mg/mL in specific formulations. Pirfenidone (amounts are outlined in Table 6)

was reconstituted with 100 mL vehicle as described and mixed thoroughly by agitation. The sample was agitated until completely dissolved. Once dissolved, samples were filtered via syringe through a 0.22 µm PVDF filter.

Samples were refrigerated to reduce evaporative loss of volatile co-solvents (ethanol) during filtration and dispensing. An approximate 5.0-mL aliquot of each formulation was transferred to class A glass 6 ml containers with suitable closures (20 mm stopper). At least 8 containers are being maintained in the upright orientation at 25°C/60RH, and another 8 containers maintained at 40 °C/75RH. One container for each formulation was used for the initial evaluation, t=0, with testing for: appearance, pH, osmolality, HPLC = RP-HPLC for pirfenidone assay (reported as % label claim) and individual impurities (reported as % pirfenidone and RRT). Stability time point testing will evaluate for appearance, and HPLC = RP-HPLC for pirfenidone assay (reported as % label claim) and individual impurities (reported as % pirfenidone and RRT).

Table 6. Representative Pirfenidone Formulations for Stability Assessment

Target 5 mM Phosphate Buffer, pH 6.5, plus	Target Pirfenidone (mg/mL)	Add Pirfenidone (mg)	Add Buffer (mL)	Add Ethanol (mL)	Add PG (mL)
8% (v/v) EtOH, 16% (v/v) PG	38	3800	20	8.0	16.0
8% (v/v) EtOH, 16% (v/v) PG	1	100	20	8.0	16.0
6% (v/v) EtOH, 12% (v/v) PG	30	300	20	6.0	12.0
4% (v/v) EtOH, 8% (v/v) PG	23	230	20	4.0	8.0
1% (v/v) EtOH, 2% (v/v) PG	15	150	20	1.0	2.0
1% (v/v) EtOH, 2% (v/v) PG	1	100	20	1.0	2.0

For each variant Formulation, samples are tested according to the schedule shown in Table 7.

Table 7. Stability Schedule

Condition	Tests* Performed at Time Point (mo) =								total
	0	0.5**	1	3	6	9	12	contingency	
25 °C/60 %RH	1	1	1	1	1	1	1	2	9
40 °C/75 %RH		1	1	1	1	1	1	2	8

* all samples will be tested for appearance by visual observation, pH, HPLC = RP-HPLC for pirfenidone assay (reported as % label claim), and individual impurities (reported as % pirfenidone and RRT). At t=0, testing will also include osmolality.

** Appearance only

2012212269 02 May 2016

Table 8. Time-Zero Stability Assessment

Target 5 mM Phosphate Buffer, pH 6.5, plus	Target Pirfenidone (mg/mL)	Measured Pirfenidone (mg/mL)	pH	mOsmol/kg	App.
8% (v/v) EtOH, 16% (v/v) PG	38	38.9	7.04	3750	*
8% (v/v) EtOH, 16% (v/v) PG	1	1.0	6.98	3590	*
6% (v/v) EtOH, 12% (v/v) PG	30	30.3	6.90	2863	*
4% (v/v) EtOH, 8% (v/v) PG	23	24.1	6.78	1928	*
1% (v/v) EtOH, 2% (v/v) PG	15	16.1	6.65	512	*
1% (v/v) EtOH, 2% (v/v) PG	1	1.0	6.69	452	*

* All solutions are clear and colorless without visible signs of crystallization.

Selected formulations were prepared for pharmacokinetic analysis following aerosol
 5 delivery to rat lung. In these studies, lung, heart, kidney and plasma tissue samples were
 analyzed for pirfenidone and metabolite content (Tables 16-19). Formulations prepared for
 this study are outlined in Table 9. Briefly, this study prepared pirfenidone in 5 mM sodium
 phosphate buffer, pH 6.5, as a function of optimized co-solvent strength. The target
 concentration in each formulation is 12.5 mg/mL. Pirfenidone (amounts as described in
 10 Table 9) were reconstituted with 30 mL vehicle as described and mixed thoroughly by
 agitation. The sample was agitated until completely dissolved. Once pirfenidone had
 dissolved completely, formulations were filtered via syringe through a 0.22 µm PVDF filter.
 Filtered samples were analyzed by HPLC.

The samples were then refrigerated to reduce evaporative loss of volatile co-solvents
 15 (ethanol) during filtration and dispensing. Formulations were transferred to class A glass
 containers (approximately 10 mL) with suitable closures (20 mm stopper).

2012212269 02 May 2016

Table 9. Formulations for Co-Solvent Effects Pharmacokinetic and Tissue Distribution Study

Dosing Group	Target 5 mM Phosphate Buffer, pH 6.5, plus	Vol. (mL) *	Target Pirfenidone (mg/mL)	Add Pirfenidone (mg)	Add Buffer* (mL)	Add EtOH (mL)	Add PG (mL)	Add NaCl (g)
1	8% (v/v) EtOH, 16% (v/v) PG	30	12.5	375	6	2.4	4.8	0
2	6% (v/v) EtOH, 12% (v/v) PG	30	12.5	375	6	1.8	3.6	0
3	4% (v/v) EtOH, 8% (v/v) PG	30	12.5	375	6	1.2	2.4	0
4	2% (v/v) EtOH, 4% (v/v) PG	30	12.5	375	6	0.6	1.2	0
5	1% (v/v) EtOH, 2% (v/v) PG	30	12.5	375	6	0.3	0.6	0
6	0.4% NaCl	30	12.5	375	6	0	0	0.12

* Pirfenidone was reconstituted with 30 mL of the indicated Vehicle by QS'ing the remaining volume with water.

5 ** 25mM NaPO₄, pH 6.5 (5X solution)

Example 4: Nebulization Device Performance

Selected formulations were prepared for nebulization device aerosol characterization. Briefly, this study prepared pirfenidone in 5 mM sodium phosphate buffer, pH 6.5, as a function of optimized co-solvent strength. These formulations are outlined in Table 10. Pirfenidone (amounts as listed in Table 10) were reconstituted as described and mixed thoroughly by agitation. Each sample was agitated until completely dissolved. Once dissolved completely, formulations were filtered via syringe through a 0.45 µm PVDF filter. Filtered samples were analyzed by HPLC.

Each sample was refrigerated to reduce evaporative loss of volatile co-solvents (ethanol) during filtration and dispensing. As described in Table 10, each formulation was transferred to class A glass containers with suitable closures.

2012212269 02 May 2016

Table 10. Formulations for Nebulization Device Aerosol Performance Studies

Test Article	Target 5 mM Phosphate Buffer, pH 6.5, plus	Vol. (mL)	Target Pirfenidone (mg/mL)	Add Pirfenidone (mg)	Add Buffer* (mL)	Add Ethanol (mL)	Add PG (mL)	Add NaCl (g)
1	8% (v/v) EtOH, 16% (v/v) PG	200	38**	7600	40	16	32	0
2	8% (v/v) EtOH, 16% (v/v) PG	200	0	0	40	16	32	0
3	1% (v/v) EtOH, 2% (v/v) PG	200	0	0	40	2	4	0
4	0.2% (v/v) EtOH, 0.4% (v/v) PG	NA	0.475	Diluted Test Articles 1 and 3				
5	0.4% NaCl	200	0	0	40	0	0	0.8

* 25mM NaPO₄, pH 6.5 (5X solution)

** Active formulations were diluted with water and vehicle by the device characterization facility as necessary to characterize lower pirfenidone concentrations.

Philips I-neb® AAD System

For aerosol analysis, three units of each I-neb breath-actuated nebulizer were studied in triplicate for each device/formulation combination. Using Malvern Mastersizer aerosol particle sizer, the particle size and distribution was characterized. Parameters reported were mass median diameter (MMD), span, fine particle fraction (FPF= % ≤ 5 microns), output rate (mg formulation per second), nebulized volume, delivered volume (volume of dose in range of FPF), respirable delivered dose (mg pirfenidone delivered volume). Aerosol output was measured using a 5 second inhalation, 2 second exhalation breathing pattern with a 1.25 L tidal volume. The results are shown in Table 11.

2012212269 02 May 2016

Table 11. Nebulization of Pirfenidone Formulations using the Philips I-neb Device

Parameter	Test Article 1	Test Article 2	Test Article 3	Test Article 4	Test Article 5
MMD (micron)	3.31	3.64	4.95	5.52	4.95
Span (micron)	1.13	1.36	1.21	1.14	1.20
FPF (% < 5 microns)	84.41	74.70	51.40	42.01	51.11
Output rate (mg/sec)	0.96	1.31	3.52	6.92	4.60
Nebulized vol (mg)	776.63	810.42	846.42	853.30	814.51
Delivered vol (mg)	653.44	605.83	436.19	345.55	417.12
RDD (mg)*	24.83	NA	NA	0.16	NA

* Exemplary (RDD = FPF X Nebulized Volume x loaded dose)

PARI eFlow® – 35 head

- 5 For aerosol analysis, three units of each eFlow nebulizer containing a 35-head were studied in duplicate for each device/formulation combination. Using an Insittec Spraytec Laser Particle sizer, the particle size and distribution was characterized. Parameters reported were volumetric mean diameter (VMD), geometric standard deviation (GSD), time to nebulize dose (duration), remaining dose following nebulization (dead volume), and fine
- 10 particle fraction (FPF= % ≤ 5 microns). 4 mL of each formulation was tested. The results are shown in Table 12.

Table 12. Nebulization of Pirfenidone Formulations using the PARI eFlow Device

Parameter	Test Article 1	Test Article 2	Test Article 3	Test Article 4	Test Article 5
Loaded Dose (mg)	152	0	0	1.9	0
VMD (micron)	2.60	2.84	3.60	3.88	3.81
GSD (micron)	1.86	1.85	1.74	1.68	1.68
FPF (% < 5 microns)	85.47	81.81	71.26	67.70	68.78
Duration (min)	9.87	8.85	6.26	5.99	5.86
Dead volume (mL)	0.15	0.16	0.19	0.18	0.16
Output rate (mL/min)	0.40	0.44	0.61	0.64	0.67
Nebulized vol (mL)	3.85	3.84	3.81	3.82	3.84
RDD (mg)*	87.04	NA	NA	0.86	NA
RDD (mg)/minute	8.82	NA	NA	0.14	NA

- * Exemplary (RDD = FPF X Inhaled Mass X Loaded Dose). For the exemplary calculation, assume a 67% delivered dose (i.e. inhaled mass). (Representative of a 1:1 inhalation:exhalation breathing pattern using the eFlow device with 35 head.)
- 15

Aerogen Aeroneb® Solo

For aerosol analysis, between two and four units of each Aeroneb® Solo nebulizer with Aeroneb® Pro-X controller were studied with each formulation. Using a Malvern Spraytech aerosol particle sizer, the particle size and distribution were characterized.

Parameters reported were volumetric mean diameter (VMD), geometric standard deviation (GSD), time to nebulize dose (duration), remaining dose following nebulization (dead volume), and fine particle fraction (FPF= % \leq 5 microns). 1 mL of each formulation was tested. The results are shown in Table 13.

Table 13. Nebulization of Pirfenidone Formulations using the Aeroneb Solo Device

Parameter	Test Article 1	Test Article 2	Test Article 3	Test Article 5
Loaded Dose (mg)	38	0	0	0
VMD (micron)	9.73	5.49	4.31	4.76
GSD (micron)	3.21	3.43	2.25	2.23
FPF (% $<$ 5 microns)	38.97	48.13	59.09	53.77
Duration (min)	5.88	5.56	4.17	2.17
Output rate (mL/min)	0.17	0.18	0.24	0.46
RDD (mg)*	9.9	NA	NA	NA
RDD (mg)*/minute	1.68	NA	NA	NA

* Exemplary (RDD = FPF X Inhaled Mass X Loaded Dose). For the exemplary calculation, assume a 67% inhaled mass.

Example 5. Process temperature Development study

This study examined the above-ambient temperature stability of pirfenidone in aqueous solution to best understand stability at this temperature and saturation solubility. This information may be utilized with manufacturing process embodiments of the present invention wherein high temperature pirfenidone aqueous dissolution, in the presence of or followed by co-solvent and/or surfactant and/or cation addition, and subsequent cooling to ambient temperature provide higher pirfenidone saturation solubility than ambient temperature dissolution alone. In this process, added co-solvent and/or surfactant and/or cation may stabilize the high-temperature-dissolved pirfenidone during the cooling process and provide a stable, high-concentration, ambient-temperature formulation for long-term storage. Alternatively, the added co-solvent and/or surfactant and/or cation may provide access to greater soluble pirfenidone for which to maintain in solution than ambient

02 May 2016
2012212269

temperature dissolution alone. Alternatively, high-temperature dissolution may be integrated into manufacturing process embodiments to reduce dissolution time and/or reduce the effects of lot-to-lot crystal structure, amorphous content and polymorph variability on dissolution time and degree of dissolution.

5 Formulations were prepared as described in Table 11. Briefly, this study prepared 250 mg pirfenidone in 5 mM sodium phosphate buffer, pH 6.5, in the presence of ethanol, propylene glycol and/or polysorbate 80. The final volume of each formulation was 5 mL. Pirfenidone (amounts as listed in Table 11) were reconstituted as described and mixed thoroughly by agitation. Each sample was mixed thoroughly and agitated overnight at 60°C. 10 Rapid cooling and step-wise cooling from 60°C to 25°C was performed. HPLC analysis was performed on samples taken after overnight incubation and after cooling to 25°C. Prior to HPLC analysis, formulations were filtered via syringe through a 0.45 µm PVDF filter. Results for this evaluation are shown in Table 14.

15

20

25

30

2012212269 02 May 2016

Table 14. Formulations for Process Temperature Study

Added Co-Solvent and/or Surfactant (% v/v)			%Phosphate Buffer (5 mM)	pH	Pirfenidone (mg/mL)		Observations
EtO H	PG	PS80			60°C ^a	Re- crystal ^b	
4	8	0	88	6.7	50.3 4	27.6	Fully dissolved after overnight at 60°C. Stable at 25°C for >4 hours before re-crystallization
4	8	0.04	88	6.7	51.8	26.8	Fully dissolved after overnight at 60°C. Stable at 25°C for >4 hours before re-crystallization
4	0	0.04	96	6.6	50.7	22.4	Fully dissolved after overnight at 60°C. Stable at 25°C for >4 hours before re-crystallization
0	8	0.04	92	6.7	52.8	22.3	Fully dissolved after overnight at 60°C. Stable at 25°C for >4 hours before re-crystallization
0	8	0	92	6.6	54.6	18.6	Fully dissolved after overnight at 60°C. Stable at 25°C for >4 hours before re-crystallization

- a. Pirfenidone assay content after stepwise cooling to 25°C
- b. Pirfenidone assay content after stepwise cooling to 25°C and then later re-crystallization
- c. Calculated
- d. Not determined
- e. Pirfenidone concentration at 85% saturation solubility
- f. Crystals re-dissolved at 25°C without agitation

The results in Table 14 show that heating pirfenidone to 60°C enables full dissolution up to or potentially greater than 50 mg/mL. Rapid cooling to 25°C of this dissolved material led to rapid recrystallization (data not shown). Slow cooling to 25°C (step-wise from 60°C to 40°C to 30°C then 25°C, with temperature equilibration occurring at each step prior to further reducing the temperature) enabled pirfenidone to stay in solution at about 50 mg/mL for several hours before each solution ultimately re-crystallized. Filtering each formulation prior to re-crystallization (either at 30°C or after equilibrium at 25°C) did not noticeably extend or prevent re-crystallization. Pirfenidone dissolution time is reduced by heating and appears to be stable at this temperature during the dissolution process. Thus, heating pirfenidone formulations can be beneficial in a manufacturing process embodiments to overcome the slower dissolution observed at ambient temperature.

Example 6: Pharmacokinetics and Lung-Tissue Distribution

Sprague-Dawley rats (300-350 grams) were administered pirfenidone by either the oral (gavage) or aerosol (intratracheal Penn Century nebulizing catheter) routes. For oral administration, 50 mg pirfenidone was dissolved in 3.33 mL distilled water containing 0.5% CMC to a final concentration of 15 mg/mL. Solutions were vortexed until all crystals dissolved. Rats were administered 70 mg/kg pirfenidone (~ 1.4 mL). Plasma samples were taken at pre-dose, 0.08, 0.16, 0.25, 0.5, 0.75, 1.0, 1.5, 2, 4, and 6 hours post dosing. For lung tissue samples, eight additional rats were also dosed 70 mg/kg by the oral route. Lungs were taken at pre-dose 0.08, 0.5, 2, and 4 hours post dosing. Materials were extracted and pirfenidone quantitated as µg/mL plasma and µg/gram lung tissue. For aerosol administration, 60 mg pirfenidone was dissolved in 10 mM phosphate buffer, pH 6.2 containing 81 mM MgCl₂ (1:1 pirfenidone to magnesium). Rats were administered 5 mg/kg pirfenidone (~100 µL) by nebulizing catheter. Plasma samples were taken at pre-dose, 0.08, 0.16, 0.25, 0.5, 0.75, 1.0, 1.5, 2, 4, and 6 hours post dosing. For lung tissue samples, eight additional rats were also dosed 70 mg/kg by the oral route. Lungs were taken at pre-dose 0.08, 0.5, 2, and 4 hours post dosing. Materials were extracted and pirfenidone quantitated as µg/mL plasma and µg/gram lung tissue. Results from these studies are shown in Table 15.

2012212269 02 May 2016

Table 15. Pirfenidone pharmacokinetics and tissue distribution following oral and aerosol administration to rats.

		Aerosol Measured ^a		Oral
Rat dose (mg/kg)		1	5	70
Lung	C _{max} ^b	101	508	3.6
	T _{1/2} ^c	<1, 45	<1, 45	45
	AUC ^d	5.2	25.4	4.3
	TOE ^e	5	84	89
Plasma	C _{max} ^f	1.1	7.0	8.1
	T _{1/2}	30	30	30
	AUC _{0-6hrs} ^g	0.9	4.5	13.5

- a. Bolus aerosol intratracheal delivery
b. C_{max}: Lung tissue (µg/g) immediate post-dose calculated from the direct-lung delivered dose. All other time points measured. Plasma measured (µg/mL)
c. T_{1/2}: Minutes (aerosol = α, β; oral = α only observed)
d. AUC: Lung tissue (mg·hr/kg for time >1 µg/g)
e. TOE: Time of exposure as minutes over 1 µg/g lung tissue)
f. C_{max}: Plasma (µg/mL)
g. AUC_{0-6hrs}: Plasma (mg·hr/L)

5 **Example 7: Pharmacokinetics and Tissue Distribution of Co-solvent Formulations**

To assess the pharmacokinetics and tissue distribution of co-solvent formulations (described in Table 9), Sprague-Dawley rats (350-400 grams) in triplicate were administered pirfenidone by bolus aerosol (intratracheal Penn Century nebulizing catheter). Rats were dosed about 4 mg/kg pirfenidone (~150 µL) by nebulizing catheter. Plasma samples, and entire lungs, hearts and kidneys were taken at pre-dose, 0.033, 0.067, 0.1, 0.167, 0.333, 0.667, 1.0, 1.5, 2, and 2.5 hours post dosing. Materials were extracted and pirfenidone quantitated as µg/mL plasma and µg/gram lung, heart or kidney tissue. Results from these studies are shown in Table 16 thru 19. No adverse events were noted in these studies.

2012212269 02 May 2016

Table 16. Pirfenidone Pharmacokinetics and Lung Tissue Distribution - Co-Solvent-Based Formulation Study (Dosing group formulations listed in Table 9)

Analyte	Time (hr)	Group 1	Group 2	Group 3	Group 4	Group 5	Group 6
		Mean µg/gram	Mean µg/gram	Mean µg/gram	Mean µg/gram	Mean µg/gram	Mean µg/gram
PIRFENIDONE	0 ^A	107.58					
	0.0333	3.57	3.93	5.56	3.16	5.24	2.25
	0.0667	2.66	2.16	2.29	1.94	2.68	2.06
	0.1	1.93	1.49	1.84	1.87	1.51	1.71
	0.167	1.38	1.43	1.54	1.31	1.45	1.31
	0.333	1.07	0.95	0.95	1.00	1.27	0.96
	0.667	0.52	0.60	0.61	0.62	0.48	0.57
	1	0.38	0.31	0.26	0.34	0.36	0.31
	1.5	0.15	0.18	0.11	0.17	0.12	0.09
	2	0.07	0.09	0.08	0.05	0.07	0.08
	2.5	0.02	0.03	0.03	0.03	0.02	0.05
5-CARBOXY-N-phenyl-5-1H-pyridone	0 MIN	0.00					
	0.0333 H	0.03	NOT TESTED	0.03	NOT TESTED	0.07	0.04
	0.0667 H	0.03		0.10		0.10	0.11
	0.100 H	0.12		0.14		0.09	0.09
	0.167 H	0.13		0.22		0.14	0.16
	0.333 H	0.25		0.27		0.36	0.24
	0.667 H	0.24		0.20		0.24	0.23
	1 H	0.18		0.17		0.19	0.20
	1.50 H	0.12		0.13		0.11	0.11
	2 H	0.05		0.08		0.05	0.06
	2.50 H	0.03		0.03		0.02	0.04

a. Average of 18 immediate post-dose measurements

2012212269 02 May 2016

Table 17. Pirfenidone Plasma Pharmacokinetics - Co-Solvent-Based Formulation Study (Dosing group formulations listed in Table 9)

Analyte	Time (hr)	Group 1	Group 2	Group 3	Group 4	Group 5	Group 6
		Mean µg/mL	Mean µg/mL	Mean µg/mL	Mean µg/mL	Mean µg/mL	Mean µg/mL
PIRFENIDONE	0	0.03	0.01	0.06	0.01	0.02	0.06
	0.0333	6.80	6.20	7.47	7.23	7.72	6.84
	0.0667	6.09	6.04	6.52	7.43	7.05	7.31
	0.1	5.72	5.12	5.39	3.98	5.55	5.75
	0.167	5.56	5.60	5.51	4.75	4.59	5.31
	0.333	3.94	4.53	4.53	3.98	3.84	4.26
	0.667	2.74	3.02	2.54	2.41	2.24	2.87
	1	1.93	1.65	1.39	1.45	1.68	1.49
	1.5	0.67	0.80	0.54	0.85	0.59	0.43
	2	0.29	0.37	0.36	0.22	0.29	0.33
	2.5	0.09	0.12	0.11	0.11	0.08	0.13

Table 18. Pirfenidone Pharmacokinetics and Heart Tissue Distribution - Co-Solvent-Based Formulation Study (Dosing group formulations listed in Table 9)

Analyte	Time (hr)	Group 1	Group 2	Group 3	Group 4	Group 5	Group 6
		Mean µg/gram	Mean µg/gram	Mean µg/gram	Mean µg/gram	Mean µg/gram	Mean µg/gram
PIRFENIDONE	0	0.00	0.05	NOT TESTED			0.02
	0.0667	1.97	1.48				1.58
	0.167	1.23	1.02				1.24
	0.333	0.96	0.78				0.86
	0.667	0.45	0.55				0.55
	1	0.35	0.27				0.31
	1.5	0.15	0.17				0.09
	2.5	0.02	0.03				0.03

2012212269 02 May 2016

Table 19. Pirfenidone Pharmacokinetics and Kidney Tissue Distribution - Co-Solvent-Based Formulation Study (Dosing group formulations listed in Table 9)

Analyte	Time (hr)	Group 1	Group 2	Group 3	Group 4	Group 5	Group 6
		Mean µg/gram	Mean µg/gram	Mean µg/gram	Mean µg/gram	Mean µg/gram	Mean µg/gram
PIRFENIDONE	0	0.00	0.13	NOT TESTED			0.08
	0.0667	2.65	2.87				3.42
	0.167	1.70	2.21				1.74
	0.333	1.30	2.02				1.23
	0.667	0.74	0.84				0.88
	1	0.51	0.46				0.43
	1.5	0.26	0.24				0.15
	2.5	0.05	0.05				0.05

Results from the co-solvent effects tissue distribution studies show that the presence of up to 8% ethanol with 16% propylene glycol to change the tissue or plasma

5 pharmacokinetic profile compared to a 0.4% sodium chloride formulation. Further, these results show a delayed appearance of 5-Carboxy-pirfenidone (the primary pirfenidone liver metabolite). Comparing the initial rapid elimination of pirfenidone from the lung tissue and parallel appearance of pirfenidone in the plasma suggest that direct pulmonary administration may be a good route for systemic administration of pirfenidone. The delayed appearance of

10 5-Carboxy-pirfenidone metabolite supports this hypothesis in that this metabolite serves as a marker for re-circulation of pirfenidone to the lung and other tissues following direct aerosol administration to the lung. Further, as suggested in Tables 15 and 16 and supported by the modeled data in Figure 1 and Table 20, re-circulated pirfenidone is likely important to support long-term, elevated pirfenidone levels in the lung and other tissues of potential

15 efficacy.

To understand pirfenidone human lung tissue distribution and associated pharmacokinetics following a 10-12 minute aerosol administration from a nebulizer, measured rat pharmacokinetic and lung tissue distribution data following bolus nebulizing catheter administration was scaled. Briefly, using allometric scaling, rat aerosol lung data

20 and plasma delivery was scaled to humans. Rat data was taken from Table 16 and 17. Allometric scaling used parameters established in the US FDA Guidance for Industry -

02 May 2016
2012212269

Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers. July, 2005, and Caldwell et al., European Journal of Drug Metabolism and Pharmacokinetics, 2004, Vol. 29, No.2, pp. 133-143. For comparative purposes, human plasma pharmacokinetic data resulting from oral administration was taken directly Rubino et al., 2009. For oral data, fed-state human data was used. To model plasma pirfenidone pharmacokinetics where plasma pirfenidone was delivered from aerosol administration, pharmacokinetics data from fasting-state humans was used (Rubino et al., 2009). Inhaled aerosol-derived plasma pirfenidone levels were calculated based upon an assumed 100% bioavailability of inhaled, respirable-deposited pirfenidone to a 5,000 mL total blood volume. The contribution of plasma-derived pirfenidone (whether from oral or aerosol inhalation dosing) to lung tissue distribution and pharmacokinetics assumed at any given time 50% of plasma pirfenidone was delivered to the lung tissue. By example, a plasma level of 10 µg/mL contributed 5 µg/gram pirfenidone to the lung tissue. Results of this analysis are shown in Figure 1 and Table 20.

Aerosol deliver parameters based on Table 10 formulation characterization in high-efficiency, mesh-based nebulizers (Tables 11-13). Respirable delivered dose (RDD) calculated by the product of fine particle fraction (FPF, %<5 microns) and inhaled mass. An about 110 mg RDD was calculated from a 5 mL device-loaded dose of a 40 mg/mL pirfenidone formulation (200 mg loaded dose). The FPF and inhaled mass were 85% and 67%, respectively. Inhaled mass was calculated based upon breathing pattern. A 1:1 inhalation:exhalation breathing pattern (e.g. a 2 second inhalation followed by a 2 second exhalation) using the eFlow device and 35-head is predicted to produce an inhaled mass of about 67%. From this, a 2:1 breathing pattern (e.g., a 4 second inhalation followed by a 2 second exhalation) may produce an inhaled mass between about 74% and about 80%. Using the inhaled mass of 74% and the FPF of 85%, a 200 mg device-loaded dose may produce an RDD of about 125 mg. Similarly, the inhaled mass of 80% may produce an RDD of about 136 mg from a 200 mg device-loaded dose. Continuing, a 3:1 breathing pattern (e.g., a 6 second inhalation followed by a 2 second exhalation) may produce an inhaled mass between about 80% and about 87%. Using the inhaled mass of 87% and the FPF of 85%, a 200 mg device-loaded dose may produce an RDD of about 148 mg. In some embodiments, the RDD may be further increased or decreased by additional means: by non-limiting example,

02 May 2016
2012212269

changing the device-loaded volume and/or changing the formulation pirfenidone concentration. In some embodiments, increasing the formulation concentration to 50 mg/mL and using the 5 mL device-loaded volume will provide a 250 mg device-loaded dose. Using the FPF of 85% and inhaled mass of about 67%, a 250 mg device-loaded dose may produce an RDD of about 142 mg, a 74% inhaled mass may produce an RDD of about 157 mg, a 80% inhaled mass may produce an RDD of about 170 mg, and a 87% inhaled mass may produce an RDD of about 185 mg. Additional dose escalations are possible with increased co-solvent addition to the pirfenidone formulation. Similarly, dose de-escalations are possible with reduced device-loaded dose (reduced volume and/or reduced pirfenidone formulation concentration) and/or less-efficient breathing pattern. While allometric scaling is an established means to predict pharmacokinetic parameters and dose scaling between animals and humans, precedent exists that supports human-inhaled therapies remaining in the lung significantly longer than the duration predicted by allometric scaling. This possibility may also result in longer lung pirfenidone residence time and may also translate to reduced plasma exposure.

Table 20. Modeled human pirfenidone pharmacokinetics and tissue distribution.

Parameter	Aerosol (RDD ^a)						Oral (801 mg)			
	110 mg		154 mg		185 mg		Fed-State		Fasted-State	
	LT	P	LT	P	LT	P	LT	P	LT	P
C _{max} ^b	57.5	17.7	71.2	24.8	85.8	30.0	3.9	7.9	7.1	14.2
AUC ^c	43.4	68.9	61.0	96.8	75.1	118.3	22.1	58.9	33.9	67.7
TOE ^d	8.7	–	9.9	–	10.4	–	10.4	–	10.0	–
T _{1/2} alpha (min)	5	–	5	–	5	–	–	–	–	–
T _{1/2} beta (hr) ^e	2.5	2.5	2.5	2.5	2.5	2.5	2.4	2.4	2.5	2.5
T _{1/2} Absorption (hr) ^f	–	0.1	–	0.1	–	0.1	–	1.8	–	0.4

LT = lung tissue; P = plasma.

a. RDD: respirable delivered dose = fine particle fraction (FPF; %particles <5 microns) X inhaled mass

5 b. C_{max}: Lung tissue = microgram/gram; plasma = microgram/mL

c. AUC: Expressed as AUC over 0-18 hours, Lung tissue in mg·hr/kg and plasma expressed in mg·hr/L.

d. TOE: Time of exposure measured as minutes over 1 microgram/gram lung tissue

10 e. T_{1/2} beta: Lung tissue pirfenidone levels and associated beta phase lung tissue T_{1/2} derived solely from plasma-pirfenidone and hence, plasma pirfenidone T_{1/2}. Aerosol = Rubino et al., 2009 fasted-state; Oral = Rubino et al., 2009

f. T_{1/2} absorption: Aerosol = modeled from allometrically-scaled bolus aerosol rat data; Oral = Rubino et al., 2009.

15 The various embodiments described above can be combined to provide further embodiments. All of the U.S. patents, U.S. patent application publications, U.S. patent applications, foreign patents, foreign patent applications and non-patent publications referred to in this specification are incorporated herein by reference, in their entirety. Aspects of the

20 applications and publications to provide yet further embodiments. These and other changes can be made to the embodiments in light of the above-detailed description. In general, in the following claims, the terms used should not be construed to limit the claims to the specific embodiments disclosed in the specification and the claims, but should be construed to include all possible embodiments along with the full scope of equivalents to which such claims are

25 entitled. Accordingly, the claims are not limited by the disclosure.

02 May 2016

2012212269

The term “comprising” as used in this specification and claims means “consisting at least in part of”. When interpreting statements in this specification and claims which include “comprising”, other features besides the features prefaced by this term in each statement can also be present. Related terms such as “comprise” and “comprised” are to be interpreted in a similar manner.

5

In this specification, where reference has been made to patent specifications, other external documents, or other sources of information, this is generally for the purpose of providing a context for discussing the features of the invention. Unless specifically stated otherwise, reference to such external documents is not to be construed as an admission that such documents, or such sources of information, in any jurisdiction, are prior art, or form any part of the common general knowledge in the art.

10

2012212269 02 May 2016

CLAIMS

WHAT IS CLAIMED IS:

1. A method of prophylaxis and/or treatment of an interstitial lung disease and/or a pulmonary fibrotic disease in a human, the method comprising administration to the lungs of the human of an aqueous pharmaceutical composition comprising pirfenidone, water and one or more additional ingredients selected from co-solvents, tonicity agents, sweeteners, surfactants, wetting agents, chelating agents, anti-oxidants, salts, and buffers, wherein the pH is between pH 4.0 and pH 8.0 and the concentration of pirfenidone in the aqueous pharmaceutical composition is between 0.1 mg/mL and 100 mg/mL.
2. The method of claim 1, wherein the aqueous pharmaceutical composition is adapted for nebulized inhalation for administration to the lungs by nebulized inhalation.
3. The method of claim 1 or claim 2, wherein the aqueous pharmaceutical composition comprises a citrate buffer or a phosphate buffer.
4. The method of claim 1, 2 or 3, wherein the aqueous osmolality of the aqueous pharmaceutical composition is from about 100 mOsmol/kg to about 6000 mOsmol/kg.
5. The method of any one of claims 1-4, wherein the aqueous pharmaceutical composition comprises one or more salts selected from tonicity agents and/or wherein the aqueous pharmaceutical composition comprises saccharin.
6. The method of any one of claims 1-5, wherein the pharmaceutical composition is in a unit dosage form adapted for use in a liquid nebulizer comprising from 0.5 mL to 6 mL of an aqueous solution, and wherein the concentration of pirfenidone in the aqueous solution is from 0.1 mg/mL to 60 mg/mL.
7. The method of claim 6, wherein:
the aqueous solution further comprises one or more additional ingredients selected from co-solvents, tonicity agents, sweeteners, surfactants, wetting agents, chelating agents, anti-oxidants, salts, and buffers; and
the osmolality of the aqueous solution is from 50 mOsmol/kg to 6000 mOsmol/kg.
8. A kit comprising:
a unit dosage form of a pharmaceutical composition, the composition comprising an aqueous solution comprising pirfenidone, water and one or more additional ingredients selected from co-solvents, tonicity agents, sweeteners, surfactants, wetting agents,

02 May 2016
2012212269

chelating agents, anti-oxidants, salts, and buffers, wherein the pH is between pH 4.0 and pH 8.0, wherein the unit dosage form is adapted for use in a liquid nebulizer, and wherein the concentration of pirfenidone in the aqueous solution is from 0.1 mg/mL to 60 mg/mL, in a container that is adapted for use in a liquid nebulizer; when used for nebulized administration of the pharmaceutical composition to the lungs of a human.

9. The method of claim 2, wherein:
 - the nebulizer is a jet nebulizer, an ultrasonic nebulizer, a pulsating membrane nebulizer, a nebulizer comprising a vibrating mesh or plate with multiple apertures, or a nebulizer comprising a vibration generator and an aqueous chamber; wherein the liquid nebulizer:
 - (i) achieves lung deposition of at least 7% of pirfenidone in a human;
 - (ii) provides a Geometric Standard Deviation (GSD) of emitted droplet size distribution of the aqueous solution of 1.0 μm to 2.5 μm ;
 - (iii) provides: a) a mass median aerodynamic diameter (MMAD) of droplet size of the aqueous solution emitted with the high efficiency liquid nebulizer of 1 μm to 5 μm ;
 - b) a volumetric mean diameter (VMD) of 1 μm to 5 μm ; and/or
 - c) a mass median diameter (MMD) of 1 μm to 5 μm ;
 - (iv) provides a fine particle fraction (FPF= % \leq 5 μm) of droplets emitted from the liquid nebulizer of at least 30%;
 - (v) provides an output rate of at least 0.1 mL/min; and/or
 - (vi) provides at least 25% of the aqueous solution to the mammal.
10. An inhalation system for administration to a human of a pharmaceutical composition, the composition comprising an aqueous solution comprising pirfenidone, water and one or more additional ingredients selected from co-solvents, tonicity agents, sweeteners, surfactants, wetting agents, chelating agents, anti-oxidants, salts, and buffers, wherein the pH is between pH 4.0 and pH 8.0 and the concentration of pirfenidone in the aqueous solution is between 0.1 mg/mL and 100 mg/mL, the system comprising:
 - (a) 0.5 mL to 6 mL of the aqueous solution of pirfenidone; and

02 May 2016
2012212269

- (b) a high efficiency liquid nebulizer;
when used for nebulized administration of the pharmaceutical composition to the lungs of the human.
11. The inhalation system of claim 10, wherein the aqueous solution of pirfenidone is adapted for nebulized inhalation for administration to the lungs by nebulized inhalation.
 12. The inhalation system of claim 10 or claim 11, wherein the high efficiency liquid nebulizer:
 - (i) achieves lung deposition of at least 7% of pirfenidone in a human;
 - (ii) provides a Geometric Standard Deviation (GSD) of emitted droplet size distribution of the aqueous solution of 1.0 μm to 2.5 μm ;
 - (iii) provides: a) a mass median aerodynamic diameter (MMAD) of droplet size of the aqueous solution emitted with the high efficiency liquid nebulizer of 1 μm to 5 μm ; b) a volumetric mean diameter (VMD) of 1 μm to 5 μm ; and/or c) a mass median diameter (MMD) of 1 μm to 5 μm ;
 - (iv) provides a fine particle fraction (FPF= % $\leq 5 \mu\text{m}$) of droplets emitted from the liquid nebulizer of at least 30%;
 - (v) provides an output rate of at least 0.1 mL/min; and/or
 - (vi) provides at least 25% of the aqueous solution to the mammal.
 13. The method of claim 1, wherein the pulmonary fibrotic disease is idiopathic pulmonary fibrosis.
 14. Use of an aqueous pharmaceutical composition for the manufacture of a medicament for administration to the lungs of a human for the prophylaxis and/or treatment of an interstitial lung disease and/or a pulmonary fibrotic disease, the aqueous pharmaceutical composition comprising pirfenidone, water and one or more additional ingredients selected from co-solvents, tonicity agents, sweeteners, surfactants, wetting agents, chelating agents, anti-oxidants, salts, and buffers, wherein the pH is between pH 4.0 and pH 8.0 and the concentration of pirfenidone in the aqueous pharmaceutical composition is between 0.1 mg/mL and 100 mg/mL.

2012212269 02 May 2016

15. The use of claim 14, wherein the aqueous pharmaceutical composition is adapted for nebulized inhalation for administration to the lungs by nebulized inhalation.
16. The use of claim 14 or 15, wherein the aqueous pharmaceutical composition comprises a citrate buffer or a phosphate buffer.
17. The use of claim 14, 15 or 16, wherein the aqueous osmolality of the aqueous pharmaceutical composition is from 100 mOsmol/kg to 6000 mOsmol/kg.
18. The use of any one of claims 14 to 17, wherein the aqueous pharmaceutical composition comprises one or more salts selected from tonicity agents and/or wherein the aqueous pharmaceutical composition comprises saccharin.
19. The use of any one of claims 14 to 18, wherein the medicament comprises a unit dosage adapted for use in a liquid nebulizer comprising from 0.5 mL to 6 mL of the aqueous solution, wherein the concentration of pirfenidone in the aqueous solution is from 0.1 mg/mL and 60 mg/mL.
20. The use of claim 19, wherein:
the aqueous solution further comprises one or more additional ingredients selected from co-solvents, tonicity agents, sweeteners, surfactants, wetting agents, chelating agents, anti-oxidants, salts, and buffers; and
the osmolality of the aqueous solution is from 50 mOsmol/kg to 6000 mOsmol/kg.

FIG. 1

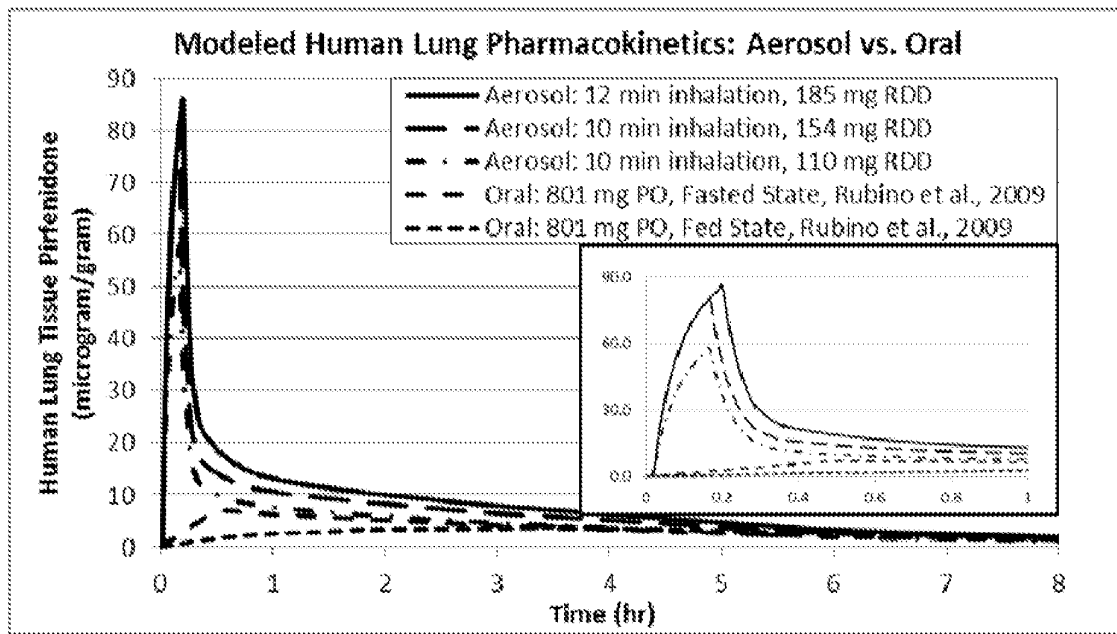


Figure 1. Modeled Nebulized Aerosol Administration to a Human.