

LPA1 ANTAGONISTS FOR TREATING INTERSTITIAL LUNG DISEASE

CROSS-REFERENCE TO RELATED APPLICATIONS

- [0001] This application claims the priority benefit of U.S. Provisional Application No. 63/476,995, filed December 23, 2022, and U.S. Provisional Application No. 63/519,703, filed August 15, 2023, which are each incorporated by reference herein in their entireties.

TECHNICAL FIELD

- [0002] This disclosure relates to methods of treating interstitial lung disease by administering an LPA₁ antagonist to the subject at one or more daily dosages lower than the standard daily dosage during a dose titration period of treatment then increasing the dosage to the standard daily dosage of the LPA₁ antagonist.

BACKGROUND

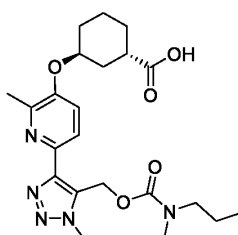
- [0003] The interstitial lung diseases (ILDs) are a group of heterogeneous lung disorders classified together based on shared clinical features, parenchymal lung scarring (fibrosis) and/or inflammation with varying patterns of lung injury by imaging or histopathology. ILD may arise due to identifiable causes such as an underlying systemic autoimmune disease (e.g., systemic sclerosis or rheumatoid arthritis), environmental exposure (e.g., asbestos or silica), or result from medication toxicity, but is often idiopathic in nature. Idiopathic pulmonary fibrosis (IPF), one of the more common and most devastating types of ILD, is a chronic, progressive, and typically fatal lung disease of unknown cause characterized by worsening dyspnea, cough, loss of lung function due to scar formation in the lung and must have the pathological and radiographic pattern known as usual interstitial pneumonia (UIP) (Meltzer et al., Orphanet J. Rare Dis. 2008, 3:8). Beyond IPF, some patients with other forms of ILD develop a progressive fibrotic phenotype, characterized by worsening respiratory symptoms, lung function, progressive fibrosis on imaging and early mortality.
- [0004] To date, two approved treatments, pirfenidone and nintedanib, significantly reduce the decline in lung function in patients with IPF and both appear to have modest effects

on progression-free survival (Noble et al., *Lancet* 2011, 377 (9779), 1760-1769; King et al., *N. Engl. J. Med.* 2014, 370 (22), 2083-2092; Richeldi et al., *New Engl J Med* 2014, 370 (22), 2071-2082). However, many patients progress despite treatment. Another treatment option is lung transplantation, which has been shown to improve mortality in carefully selected patients, but not without complications (Kistler et al., *BMC Pulmonary Med.* 2014; 14:139). Despite these advances, there remains a large unmet need for a safe, well-tolerated and effective therapy for IPF that improves pulmonary function, delays disease progression, and reduces mortality.

[0005] Because of the clinical and pathophysiological similarities among IPF and other forms of progressive pulmonary fibrosis (PPF), it has been suggested that such disorders have a common pathobiologic mechanism regardless of the cause, with resultant progressive lung fibrosis, and thus could have a similar response to treatment as IPF (Raghu et al., *Am. J. Respir. Crit. Care Med.* 2022, 205, e18-e47; du Bois et al., *Am. J. Respir. Crit. Care Med.* 2012, 186, 712-715; Flaherty et al., *N. Engl. J. Med.* 2019, 381 (18), 1718-1727). Indeed, in the recently published INBUILD trial, patients with PPF with diverse etiologies were treated with nintedanib or placebo. Those treated with nintedanib had slower progression of lung fibrosis than those who received placebo, as demonstrated by a lower annual rate of decline in forced vital capacity (FVC) over the 52-week study period (Flaherty et al., *N. Engl. J. Med.* 2019, 381 (18), 1718-1727). The absolute treatment effects in the PPF study were similar in magnitude to those observed in the pivotal IMPULSIS trials that led to approval of nintedanib for treatment of IPF. Furthermore, the IMPULSIS and INBUILD trials demonstrated that IPF and PPF patients were similar with respect to their rate of FVC decline. Based on data from the INBUILD trial, health authorities have also approved nintedanib for patients with PPF. Nonetheless, as many patients are unable to tolerate nintedanib due to gastrointestinal side effects, and because some patients may progress despite ongoing treatment with nintedanib, there remains an unmet need for well-tolerated, effective therapies for PPF (Flaherty et al., *N. Engl. J. Med.* 2019, 381 (18), 1718-1727).

[0006] Overall, there is a high unmet need for effective and tolerable treatments for patients with IPF and non-IPF, PPF that exhibit disease progression. Fibrotic diseases such as these can be mediated by LPA, which signals via six LPA receptors (LPA₁₋₆). Signalling via LPA₁ appears to be fundamental in the pathogenesis of fibrotic diseases.

- [0007] U.S. Patent Application Publication No. 2017/0360759 (PCT Application Publication No. WO2017/223016) discloses certain antagonists of lysophosphatidic acid (LPA) receptors for use in treating LPA-dependent or LPA-mediated conditions or diseases such as fibrosis of various organs, including the lung.
- [0008] The compound of (1S,3S)-3-((2-methyl-6-(1-methyl-5-(((methyl(propyl)carbamoyl)-oxy)methyl)-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (hereafter referred as to “Compound A”) is described in U.S. Patent Application Publication No. 2017/0360759.



Compound A

- [0009] Compound A is a potent LPA₁ antagonist in vitro (LPA₁ K_b = 6.9 nM in CHO cells overexpressing human LPA₁ and LPA₁ K_b = 5.9 nM in normal human lung fibroblasts). Compound A is currently in clinical development as a therapy for IPF and PF-ILD.
- [0010] The present disclosure provides methods of treating interstitial lung disease using LPA₁ antagonists.

BRIEF DESCRIPTION OF THE DRAWINGS

- [0011] FIG. 1 shows a powder X-ray diffraction (PXRD) pattern of Form A.
- [0012] FIG. 2 shows a differential scanning calorimetry (DSC) thermogram of Form A.
- [0013] FIG. 3 shows a thermogravimetric analysis (TGA) thermogram of Form A.
- [0014] FIG. 4 shows moisture sorption isotherms of Form A.
- [0015] FIG. 5 shows the effect of single ascending doses of Compound B on systolic blood pressure over time.
- [0016] FIG. 6 shows the effect of multiple ascending doses of Compound B on systolic blood pressure over time.
- [0017] FIG. 7 shows an outline of the Phase 2 trial.

- [0018] FIG. 8 shows the rate of change in ppFVC in patients treated with placebo or Compound A.
- [0019] FIG. 9 shows the change in FVC (mL) in patients treated with placebo or Compound A.
- [0020] FIG. 10 shows the absolute change from baseline in FVC (mL) in patients treated with placebo or Compound A.
- [0021] FIG. 11 shows the rate of change in ppFVC according to background antifibrotic use in patients treated with placebo or Compound A.
- [0022] FIG. 12 shows the change from baseline in ppFVC percentage (primary estimand) in PPF subjects treated with placebo or Compound A.
- [0023] FIG. 13 shows the change from baseline in FVC (mL) (primary estimand) in PPF subjects treated with placebo or Compound A.
- [0024] FIG. 14 shows the change from baseline in ppFVC percentage (primary estimand) of PPF subjects with UIP treated with placebo or Compound A.
- [0025] FIG. 15 shows the change from baseline in FVC (mL) (primary estimand) in PPF subjects without UIP treated with placebo or Compound A.
- [0026] FIG. 16 shows the rate of change in ppFVC of PPF subjects with and without UIP treated with placebo or Compound A.
- [0027] FIG. 17 shows the change from baseline in ppFVC percentage (primary estimand) of PPF subjects taking antifibrotics that were treated with placebo and Compound A.
- [0028] FIG. 18 shows the change from baseline in FVC (mL) (primary estimand) in PPF subjects not taking antifibrotics that were treated with placebo or Compound A.

SUMMARY

- [0029] In some aspects, the present disclosure provides a method of treating interstitial lung disease in a subject in need thereof, the method comprising administering an LPA₁ antagonist to the subject at one or more daily dosages lower than the standard daily dosage during a dose titration period of treatment then increasing the daily dosage to the standard daily dosage of the LPA₁ antagonist. In some aspects, the dose titration period of treatment is completed within 21 days. In some aspects, the dose titration period of treatment is completed within 14 days. In some aspects, the dose titration period of treatment is completed within 10 days. In some aspects, the dose titration period of

treatment is completed within 7 days. In some aspects, the dose titration period of treatment is completed within 5 days.

[0030] In some aspects, the dose titration period of treatment comprises an initial period of treatment and a second period of treatment. In some aspects, the initial period of treatment is completed within 7 days. In some aspects, the initial period of treatment is completed within 4 days. In some aspects, the initial period of treatment is completed within 3 days. In some aspects, the initial period of treatment is completed within 2 days. In some aspects, the initial period of treatment is completed within 1 day.

[0031] In some aspects, the second period of treatment is completed within 7 days. In some aspects, the second period of treatment is completed within 4 days. In some aspects, the second period of treatment is completed within 3 days. In some aspects, the second period of treatment is completed within 2 days. In some aspects, the second period of treatment is completed within 1 day.

[0032] In some aspects, the dose titration period of treatment further comprises a third period of treatment. In some aspects, the third period of treatment is completed within 7 days. In some aspects, the third period of treatment is completed within 4 days. In some aspects, the third period of treatment is completed within 3 days. In some aspects, the third period of treatment is completed within 2 days. In some aspects, the third period of treatment is completed within 1 day.

[0033] In some aspects, the present disclosure provides a method of treating interstitial lung disease in a subject in need thereof, the method comprising administering an LPA₁ antagonist to the subject at a daily dosage lower than the standard daily dosage during an initial period of treatment, followed by administering the dosage at a daily dosage higher than the initial period but lower than the standard daily dosage for a second period of treatment, then increasing the dosage to the standard daily dosage of the LPA₁ antagonist.

[0034] In some aspects, the initial period of treatment and the second period of treatment are each independently completed within 7 days. In some aspects, the initial period of treatment and the second period of treatment are each independently completed within 4 days. In some aspects, the initial period of treatment and the second period of treatment are each independently completed within 3 days. In some aspects, the initial period of treatment and the second period of treatment are each independently completed within 2

days. In some aspects, the initial period of treatment and the second period of treatment are each independently completed within 1 day.

[0035] In some aspects, increasing the dosage comprises administering the dosage at a daily dosage lower than the standard daily dosage for a third period of treatment, then administering the standard daily dosage for a fourth period of treatment. In some aspects, the third period of treatment is completed within 7 days. In some aspects, the third period of treatment is completed within 4 days. In some aspects, the third period of treatment is completed within 3 days. In some aspects, the third period of treatment is completed within 2 days. In some aspects, the third period of treatment is completed within 1 day.

[0036] In some aspects, the LPA₁ antagonist is administered once a day. In some aspects, the LPA₁ antagonist is administered twice a day.

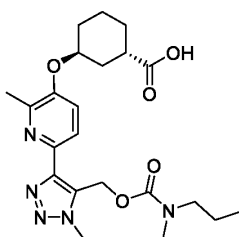
[0037] In some aspects, the LPA₁ antagonist is administered orally. In some aspects, the LPA₁ antagonist is administered as a tablet.

[0038] In some aspects, the subject is being treated with one or more additional therapies for interstitial lung disease. In some aspects, the one or more additional therapies is pirfenidone. In some aspects, the one or more additional therapies is ninedanib.

[0039] In some aspects, the LPA₁ antagonist is administered with food. In some aspects, the LPA₁ antagonist is administered without food.

[0040] In some aspects, the interstitial lung disease is idiopathic pulmonary fibrosis (IPF). In some aspects, the interstitial lung disease is progressive pulmonary fibrosis (PPF).

[0041] In some aspects, the LPA₁ antagonist is Compound A:



Compound A;

or a pharmaceutically acceptable salt thereof, and the standard daily dosage is about 120 mg/day of Compound A or an equivalent amount of a pharmaceutically acceptable salt thereof. In some aspects, the standard daily dosage of Compound A is about 60 mg twice daily or an equivalent amount of a pharmaceutically acceptable salt thereof.

[0042] In some aspects, the LPA₁ antagonist is Compound A, or a pharmaceutically acceptable salt thereof, and wherein about 20 mg/day of Compound A, or an equivalent amount of a pharmaceutically acceptable salt thereof, is administered during the initial period of treatment. In some aspects, the LPA₁ antagonist is Compound A, or a pharmaceutically acceptable salt thereof, and wherein about 10 mg twice daily of Compound A, or an equivalent amount of a pharmaceutically acceptable salt thereof, is administered during the initial period of treatment. In some aspects, the LPA₁ antagonist is Compound A, or a pharmaceutically acceptable salt thereof, and wherein about 60 mg/day of Compound A, or an equivalent amount of a pharmaceutically acceptable salt thereof, is administered during the second treatment period. In some aspects, the LPA₁ antagonist is Compound A, or a pharmaceutically acceptable salt thereof, and wherein about 30 mg twice daily of Compound A, or an equivalent amount of a pharmaceutically acceptable salt thereof, is administered during the second treatment period.

[0043] In some aspects, Compound A comprises the crystal form characterized by at least one of the following:

a) single crystal structure having unit cell parameters substantially equal to

Crystal system, space group	Triclinic, P1	
Unit cell dimensions	a = 6.53 ± 0.10 Å	alpha = 92.8 ± 1.0°
	b = 13.06 ± 0.10 Å	beta = 95.5 ± 1.0°
	c = 14.04 ± 0.10 Å	gamma = 93.0 ± 1.0°
Volume	1189(20) Å ³	
Density (calculated)	1.239 g/cm ³	
Temperature	room temperature	

wherein measurement of the single crystal structure is at room temperature;

b) a powder x-ray diffraction pattern substantially the same as shown in FIG. 1;

c) a powder x-ray diffraction pattern comprising 2 or more peaks at 2θ values selected from 6.4±0.2, 6.8±0.2, 9.6±0.2, 13.6±0.2, 15.7±0.2, 18.2±0.2, 19.9±0.2, 21.6±0.2, 24.8±0.2 and 26.8±0.2 (obtained at room temperature and CuKα λ=1.5418 Å);

d) a powder x-ray diffraction pattern comprising 3 or more peaks at 2θ values selected from 6.4±0.2, 6.8±0.2, 9.6±0.2, 13.6±0.2, 14.1±0.2, 14.5±0.2, 14.7±0.2, 15.7±0.2, 18.2±0.2, 18.7±0.2, 19.2±0.2, 19.9±0.2, 20.5±0.2, 21.6±0.2, 22.5±0.2,

23.1±0.2, 24.1±0.2, 24.8±0.2, 25.6±0.2, 26.8±0.2, 27.1±0.2 and 27.8±0.2 (obtained at room temperature and CuK α λ =1.5418 Å);

e) a differential scanning calorimetry thermogram substantially similar to the one as shown in FIG. 2;

f) a differential scanning calorimetry thermogram with an endotherm having an onset at about 152 °C; and/or

g) a thermal gravimetric analysis thermogram substantially similar to the one as shown in FIG. 3.

[0044] In some aspects, the subject experiences a smaller decline in forced vital capacity (FVC) after a treatment period compared to an untreated subject.

[0045] In some aspects, the subject experiences a greater time to first disease progression event after a treatment period than an untreated subject, wherein the first disease progression event is selected from:

absolute percentage predicted forced vital capacity (ppFVC) of $\geq 10\%$ from baseline;

acute exacerbation of lung fibrosis;

respiratory-related hospitalization;

lung transplantation; and

all-cause mortality.

[0046] In some aspects, the subject experiences a greater time to first disease progression event after a treatment period than an untreated subject, wherein the first disease progression event is selected from:

absolute predicted forced vital capacity (ppFVC) decline of $\geq 10\%$ from baseline;

acute exacerbation of lung fibrosis;

lung fibrosis-related hospitalization; and

all-cause mortality.

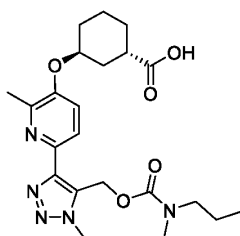
[0047] In some aspects, the subject experiences a smaller increase in cough domain score as measured by the Living with Pulmonary Fibrosis (L-PF) questionnaire over a treatment period than an untreated subject.

[0048] In some aspects, the subject experiences a smaller increase in dyspnea score as measured by the Living with Pulmonary Fibrosis (L-PF) questionnaire over a treatment period than an untreated subject.

[0049] In some aspects, the subject experiences a smaller decrease in distance traveled compared to the baseline measured by the 6-minute walk test (6MWT) over a treatment period than an untreated subject.

[0050] In some aspects which comprise a method of treating a subject with an LPA₁ antagonist for treating interstitial lung disease, the improvement comprises: reducing the incidence of cardiovascular adverse events in the subject receiving the LPA₁ antagonist by use of an initial dose escalation regimen comprising administering the LPA₁ antagonist to the subject at a daily dosage lower than the standard daily dosage during an initial period of treatment then increasing the dosage to the standard daily dosage of the LPA₁ antagonist.

[0051] In some aspects, the LPA₁ antagonist is Compound A:



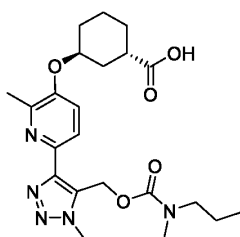
Compound A;

or a pharmaceutically acceptable salt thereof, and the standard daily dosage is about 120 mg/day of Compound A or an equivalent amount of a pharmaceutically acceptable salt thereof.

[0052] In some aspects, the interstitial lung disease is idiopathic pulmonary fibrosis (IPF). In some aspects, the interstitial lung disease is progressive pulmonary fibrosis (PPF).

[0053] In some aspects, the present disclosure provides the use of an LPA₁ antagonist for treating interstitial lung disease in a subject in need thereof, wherein the LPA₁ antagonist is administered to the subject at a daily dosage lower than the standard daily dosage during an initial period of treatment then the dosage is increased to the standard daily dosage of the LPA₁ antagonist.

[0054] In some aspects, the LPA₁ antagonist is Compound A:



Compound A;

or a pharmaceutically acceptable salt thereof, for treating interstitial lung disease and the standard daily dosage is about 120 mg/day of Compound A, or an equivalent amount of a pharmaceutically acceptable salt thereof.

[0055] In some aspects, the interstitial lung disease is idiopathic pulmonary fibrosis (IPF). In some aspects, the interstitial lung disease is progressive pulmonary fibrosis (PPF).

DETAILED DESCRIPTION

[0056] The present disclosure provides methods of treating interstitial lung disease comprising administering an LPA₁ antagonist to the subject at one or more daily dosages lower than the standard daily dosage during a dose titration period of treatment then increasing the dosage to the standard daily dosage of the LPA₁ antagonist.

[0057] In order that the present description can be more readily understood, certain terms are first defined. Additional definitions are set forth throughout the detailed description.

I. Definitions

[0058] Unless otherwise stated, the following terms used in this application, including the specification and claims, have the definitions given below. It must be noted that, as used in the specification and the appended claims, the singular forms “a,” “an,” and “the” include plural referents unless the context clearly dictates otherwise. Unless otherwise indicated, conventional methods of mass spectroscopy, NMR, HPLC, protein chemistry, biochemistry, recombinant DNA techniques and pharmacology are employed. Furthermore, use of the term “including” as well as other forms, such as “include,” “includes,” and “included,” is not limiting. The section headings used herein are for organizational purposes only and are not to be construed as limiting the subject matter described.

- [0059] All measurements are subject to experimental error and are within the spirit of the invention.
- [0060] The term “about” as used in connection with a numerical value throughout the specification and the claims denotes an interval of accuracy, familiar and acceptable to a person skilled in the art. Such interval of accuracy is $\pm 10\%$.
- [0061] The term “acceptable” with respect to a formulation, composition or ingredient, as used herein, means having no persistent detrimental effect on the general health of the subject being treated.
- [0062] The terms “administration of” and or “administering a” compound or composition should be understood to mean providing a compound or composition described herein to one or more subjects.
- [0063] As used herein, “amorphous” refers to a solid form of a molecule, atom, and/or ions that is not crystalline. An amorphous solid does not display a definitive X-ray diffraction pattern.
- [0064] The term “antagonist”, as used herein, refers to a molecule such as a compound, which diminishes, inhibits, or prevents the action of another molecule or the activity of a receptor site. Antagonists include, but are not limited to, competitive antagonists, non-competitive antagonists, uncompetitive antagonists, partial agonists and inverse agonists.
- [0065] As used herein, the term “BP” refers to blood pressure, the term “SBP” refers to systolic blood pressure and the term “DBP” refers to diastolic blood pressure.
- [0066] The terms “co-administration” or the like, as used herein, are meant to encompass administration of the selected therapeutic agents to a single subject, and are intended to include treatment regimens in which the agents are administered by the same or different route of administration or at the same or different time.
- [0067] As used herein, the term “DSC” refers to differential scanning calorimetry. The term “TGA” refers to thermogravimetric analysis.
- [0068] The terms “effective amount” or “therapeutically effective amount,” as used herein, refer to a sufficient amount of an agent or a compound being administered which will relieve to some extent one or more of the symptoms of the disease or condition being treated. The result can be reduction and/or alleviation of the signs, symptoms, or causes of a disease, or any other desired alteration of a biological system. For example, an “effective amount” for therapeutic uses is the amount of the composition comprising a

compound as disclosed herein required to provide a clinically significant decrease in disease symptoms. An appropriate “effective” amount in any individual case can be determined using techniques, such as a dose escalation study.

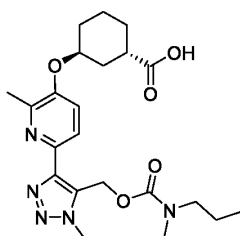
- [0069] As used herein, the phrase “pharmaceutically acceptable” refers to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.
- [0070] As used herein, “polymorphs” refer to crystalline forms having the same chemical structure but different spatial arrangements of the molecules and/or ions forming the crystals.
- [0071] The term “room temperature” generally means approximately 22°C, but can vary up or down by up to 7°C.
- [0072] The terms “subject” and “participant” are used interchangeably and encompass mammals. Examples of mammals include, but are not limited to, humans, chimpanzees, apes, monkey, cattle, horses, sheep, goats, swine, rabbits, dogs, cats, rodents, rats, mice guinea pigs, and the like. In one aspect, the mammal is a human.
- [0073] As used herein, “substantially pure,” when used in reference to a crystal form, means a compound having a purity greater than 90 weight %, including greater than 90, 91, 92, 93, 94, 95, 96, 97, 98, and 99 weight %, and also including equal to about 100 weight % of the crystal form of Compound A, based on the weight of the compound. The remaining material comprises other form(s) of the compound, and/or reaction impurities and/or processing impurities arising from its preparation. For example, a crystal form of Compound A can be deemed substantially pure in that it has a purity greater than 90 weight %, as measured by means that are at this time known and generally accepted in the art, where the remaining less than 10 weight % of material comprises other form(s) of Compound A and/or reaction impurities and/or processing impurities.
- [0074] When the term “substantially in accordance” is used in relation to PXRD, or XRPD patterns, it is to be understood that measurement of the peak locations for a given crystalline form of the same compound will vary within a margin of error. It is also to be understood that the intensities of the peaks can vary between different PXRD scans of the

same crystalline form of the same compound. The relative intensities of the different peaks are not meant to be limiting to a comparison of different PXRD scans.

- [0075] The terms “treat,” “treating,” or “treatment,” as used herein, include alleviating, abating or ameliorating at least one symptom of a disease or condition, preventing additional symptoms, inhibiting the disease or condition, *e.g.*, arresting the development of the disease or condition, relieving the disease or condition, causing regression of the disease or condition, relieving a condition caused by the disease or condition, or stopping the symptoms of the disease or condition either prophylactically and/or therapeutically.

II. Compound A

- [0076] Compound A is described in U.S. Patent Application Publication No. 2017/0360759.



Compound A

- [0077] In some aspects, Compound A comprises crystalline form “Form A.” When dissolved, a crystalline form of Compound A loses its crystalline structure, and is therefore referred to as a solution of Compound A. All forms of the present invention, however, can be used for the preparation of liquid formulations in which the drug is dissolved or suspended. In addition, the crystalline Form A of Compound A can be incorporated into solid formulations.
- [0078] As used herein, a PXRD (powder x-ray diffraction) or XRPD (x-ray powder diffraction) pattern “comprising” or having a number of peaks selected from a specified group of peaks, is intended to include PXRD patterns having additional peaks that are not included in the specified group of peaks. For example, a PXRD pattern comprising four or more peaks, preferably five or more, at 2θ values selected from: A, B, C, D, E, F, G, and H, is intended to include a PXRD pattern having: (a) four or more peaks, preferably five or more, at 2θ values selected from: A, B, C, D, E, F, G, and H; and (b) zero or more peaks that are not one of peaks A, B, C, D, E, F, G, and H.

[0079] In some aspects, Form A is characterized by a single crystal structure having unit cell parameters substantially equal to

Crystal system, space group	Triclinic, P1	
Unit cell dimensions	$a = 6.53 \pm 0.10 \text{ \AA}$	$\alpha = 92.8 \pm 1.0^\circ$
	$b = 13.06 \pm 0.10 \text{ \AA}$	$\beta = 95.5 \pm 1.0^\circ$
	$c = 14.04 \pm 0.10 \text{ \AA}$	$\gamma = 93.0 \pm 1.0^\circ$
Volume	$1189(20) \text{ \AA}^3$	
Density (calculated)	1.239 g/cm^3	
Temperature	room temperature	

wherein measurement of the single crystal structure is at room temperature.

[0080] In some aspects, Form A has a powder x-ray diffraction pattern substantially the same as shown in FIG. 1.

[0081] In some aspects, Form A has a powder x-ray diffraction pattern comprising 2 or more peaks at 2θ values selected from 6.4 ± 0.2 , 6.8 ± 0.2 , 9.6 ± 0.2 , 13.6 ± 0.2 , 15.7 ± 0.2 , 18.2 ± 0.2 , 19.9 ± 0.2 , 21.6 ± 0.2 , 24.8 ± 0.2 and 26.8 ± 0.2 (obtained at room temperature and $\text{CuK}\alpha \lambda = 1.5418 \text{ \AA}$). In some aspects, Form A has a powder x-ray diffraction comprising 3 or more peaks at 2θ values selected from 6.4 ± 0.2 , 6.8 ± 0.2 , 9.6 ± 0.2 , 13.6 ± 0.2 , 15.7 ± 0.2 , 18.2 ± 0.2 , 19.9 ± 0.2 , 21.6 ± 0.2 , 24.8 ± 0.2 and 26.8 ± 0.2 (obtained at room temperature and $\text{CuK}\alpha \lambda = 1.5418 \text{ \AA}$). In some aspects, Form A has a powder x-ray diffraction comprising 4 or more peaks at 2θ values selected from 6.4 ± 0.2 , 6.8 ± 0.2 , 9.6 ± 0.2 , 13.6 ± 0.2 , 15.7 ± 0.2 , 18.2 ± 0.2 , 19.9 ± 0.2 , 21.6 ± 0.2 , 24.8 ± 0.2 and 26.8 ± 0.2 (obtained at room temperature and $\text{CuK}\alpha \lambda = 1.5418 \text{ \AA}$).

[0082] In some aspects, Form A has a powder x-ray diffraction pattern comprising 3 or more peaks at 2θ values selected from 6.4 ± 0.2 , 6.8 ± 0.2 , 9.6 ± 0.2 , 13.6 ± 0.2 , 14.1 ± 0.2 , 14.5 ± 0.2 , 14.7 ± 0.2 , 15.7 ± 0.2 , 18.2 ± 0.2 , 18.7 ± 0.2 , 19.2 ± 0.2 , 19.9 ± 0.2 , 20.5 ± 0.2 , 21.6 ± 0.2 , 22.5 ± 0.2 , 23.1 ± 0.2 , 24.1 ± 0.2 , 24.8 ± 0.2 , 25.6 ± 0.2 , 26.8 ± 0.2 , 27.1 ± 0.2 and 27.8 ± 0.2 (obtained at room temperature and $\text{CuK}\alpha \lambda = 1.5418 \text{ \AA}$). In some aspects, Form A has a powder x-ray diffraction pattern comprising 4 or more peaks at 2θ values selected from 6.4 ± 0.2 , 6.8 ± 0.2 , 9.6 ± 0.2 , 13.6 ± 0.2 , 14.1 ± 0.2 , 14.5 ± 0.2 , 14.7 ± 0.2 , 15.7 ± 0.2 , 18.2 ± 0.2 , 18.7 ± 0.2 , 19.2 ± 0.2 , 19.9 ± 0.2 , 20.5 ± 0.2 , 21.6 ± 0.2 , 22.5 ± 0.2 , 23.1 ± 0.2 , 24.1 ± 0.2 , 24.8 ± 0.2 , 25.6 ± 0.2 , 26.8 ± 0.2 , 27.1 ± 0.2 and 27.8 ± 0.2 (obtained at room

temperature and $\text{CuK}\alpha$ $\lambda=1.5418$ Å). In some aspects, Form A has a powder x-ray diffraction pattern comprising 5 or more peaks at 2θ values selected from 6.4 ± 0.2 , 6.8 ± 0.2 , 9.6 ± 0.2 , 13.6 ± 0.2 , 14.1 ± 0.2 , 14.5 ± 0.2 , 14.7 ± 0.2 , 15.7 ± 0.2 , 18.2 ± 0.2 , 18.7 ± 0.2 , 19.2 ± 0.2 , 19.9 ± 0.2 , 20.5 ± 0.2 , 21.6 ± 0.2 , 22.5 ± 0.2 , 23.1 ± 0.2 , 24.1 ± 0.2 , 24.8 ± 0.2 , 25.6 ± 0.2 , 26.8 ± 0.2 , 27.1 ± 0.2 and 27.8 ± 0.2 (obtained at room temperature and $\text{CuK}\alpha$ $\lambda=1.5418$ Å).

[0083] In some aspects, Form A has a powder x-ray diffraction pattern comprising 2 or more peaks at 2θ values selected from 6.4 ± 0.2 , 6.8 ± 0.2 , 13.6 ± 0.2 , 15.7 ± 0.2 , and 21.6 ± 0.2 (obtained at room temperature and $\text{CuK}\alpha$ $\lambda=1.5418$ Å). In some aspects, Form A has a powder x-ray diffraction pattern comprising 3 or more peaks at 2θ values selected from 6.4 ± 0.2 , 6.8 ± 0.2 , 13.6 ± 0.2 , 15.7 ± 0.2 , and 21.6 ± 0.2 (obtained at room temperature and $\text{CuK}\alpha$ $\lambda=1.5418$ Å). In some aspects, Form A has a powder x-ray diffraction pattern comprising 4 or more peaks at 2θ values selected from 6.4 ± 0.2 , 6.8 ± 0.2 , 13.6 ± 0.2 , 15.7 ± 0.2 , and 21.6 ± 0.2 (obtained at room temperature and $\text{CuK}\alpha$ $\lambda=1.5418$ Å).

[0084] In some aspects, Form A has a differential scanning calorimetry thermogram substantially similar to the one as shown in FIG. 2.

[0085] In some aspects, Form A has a differential scanning calorimetry thermogram with an endotherm having an onset at about 152°C .

[0086] In some aspects, Form A has a thermal gravimetric analysis thermogram substantially similar to the one as shown in FIG. 3.

III. Compositions

[0087] In some aspects, the present disclosure provides compositions comprising Compound A. In some aspects, the present disclosure provides compositions comprising a crystal form of Compound A. In some aspects, the present disclosure provides compositions comprising Form A of Compound A. The term “composition” as used herein is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts. Such term in relation to pharmaceutical composition, is intended to encompass a product comprising the active ingredient(s), and the inert ingredient(s) that make up the carrier, as well as any product which results, directly or indirectly, from combination, complexation or aggregation of

any two or more of the ingredients, or from dissociation of one or more of the ingredients, or from other types of reactions or interactions of one or ignore of the ingredient.

Accordingly, the pharmaceutical compositions of the present invention encompass any composition made by mixing a compound of the present invention and a pharmaceutically acceptable carrier. By “pharmaceutically acceptable carrier” it is meant the carrier, diluent or excipient is compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

[0088] In some aspects, the compositions of the disclosure are suitable for oral administration. These compositions can comprise solid, semisolid, gelmatrix or liquid dosage forms suitable for oral administration. As used herein, oral administration includes buccal, lingual, and sublingual administration. Suitable oral dosage forms include, without limitation, tablets, capsules, pills, troches, lozenges, pastilles, cachets, pellets, medicated chewing gum, granules, bulk powders, effervescent or non-effervescent powders or granules, solutions, emulsions, suspensions, solutions, wafers, sprinkles, elixirs, syrups or any combination thereof. In some aspects, compositions of the disclosure suitable for oral administration are in the form of a tablet or a capsule. In some aspects, the compound of the disclosure can be in the form of a capsule. In some aspects, capsules can be immediate release capsules.

[0089] The compositions of the disclosure can be in the form of compressed tablets, tablet triturates, chewable lozenges, rapidly dissolving tablets, multiple compressed tablets, or enteric-coating tablets, sugar-coated, or film-coated tablets. Enteric-coated tablets are compressed tablets coated with substances that resist the action of stomach acid but dissolve or disintegrate in the intestine, thus protecting the active ingredients from the acidic environment of the stomach. Enteric-coatings include, but are not limited to, fatty acids, fats, phenylsalicylate, waxes, shellac, ammoniated shellac, and cellulose acetate phthalates. Sugar-coated tablets are compressed tablets surrounded by a sugar coating, which can be beneficial in covering up objectionable tastes or odors and in protecting the tablets from oxidation. Film-coated tablets are compressed tablets that are covered with a thin layer or film of a water-soluble material. Film coatings include, but are not limited to, hydroxyethylcellulose, sodium carboxymethylcellulose, polyethylene glycol 4000, and cellulose acetate phthalate. A film coating can impart the same general characteristics as a sugar coating. Multiple compressed tablets are compressed tablets

made by more than one compression cycle, including layered tablets, and press-coated or dry-coated tablets.

[0090] In some aspects, the compound of the disclosure can be in the form of a tablet. In some aspects, the compound of the disclosure can be in the form of a compressed tablet. In some aspects, the compound of the disclosure can be in the form of a film-coated compressed tablet. In some aspects, the compositions of the disclosure can be in the form of film-coated compressed tablets.

[0091] In some aspects, the compositions of the disclosure can be prepared by fluid bed granulation of the compound of the disclosure with one or more pharmaceutically acceptable carriers, vehicles, and/or excipients. In some aspects, the compositions of the disclosure can be prepared by fluid bed granulation process and can provide a tablet formulation with good flowability, good compressibility, fast dissolution, good stability, and/or minimal to no cracking. In some aspects, the fluid bed granulation process can allow preparation of formulations having high drug loading, such as over 70% or over 75% of a compound of the disclosure.

[0092] In some aspects, the compositions of the disclosure can be in the form of soft or hard capsules, which can be made from gelatin, methylcellulose, starch, and/or calcium alginate. The hard gelatin capsule, also known as the dry-filled capsule (DFC), can comprise two sections, one slipping over the other, thus completely enclosing the active ingredient. The soft elastic capsule (SEC) is a soft, globular shell, such as a gelatin shell, which is plasticized by the addition of glycerin, sorbitol, or a similar polyol. In some aspects, soft gelatin shells can contain a preservative to prevent the growth of microorganisms. Suitable preservatives include, but are not limited to, those as described herein, including methyl- and propyl-parabens, sorbic acid, and combinations thereof. The liquid, semisolid, and solid dosage forms provided herein can be encapsulated in a capsule. Suitable liquid and semisolid dosage forms include, but are not limited to, solutions and suspensions in propylene carbonate, vegetable oils, triglycerides, and combinations thereof. The capsules can also be coated as known by those of skill in the art in order to modify or sustain dissolution of the active ingredient.

[0093] In some aspects, the compositions of the disclosure can be in liquid or semisolid dosage forms, including emulsions, solutions, suspensions, elixirs, and syrups. In some aspects, the emulsion can be a two-phase system, in which one liquid is dispersed in the

form of small globules throughout another liquid, which can be oil-in-water or water-in-oil. Emulsions can include a pharmaceutically acceptable non-aqueous liquids or solvent, emulsifying agent, and preservative. Suspensions can include a pharmaceutically acceptable suspending agent and preservative. Aqueous alcoholic solutions can include a pharmaceutically acceptable acetal, such as a di-(lower alkyl)acetal of a lower alkyl aldehyde (the term “lower” means an alkyl having between 1 and 6 carbon atoms), e.g., acetaldehyde diethyl acetal; and a water-miscible solvent having one or more hydroxyl groups, such as propylene glycol and ethanol. Elixirs can be clear, sweetened, and hydroalcoholic solutions. Syrups can be concentrated aqueous solutions of a sugar, for example, sucrose, and can comprise a preservative. For a liquid dosage form, for example, a solution in a polyethylene glycol can be diluted with a sufficient quantity of a pharmaceutically acceptable liquid carrier, e.g., water, to be measured conveniently for administration.

- [0094] In some aspects, the compositions of the disclosure for oral administration can be also provided in the forms of liposomes, micelles, microspheres, or nanosystems.
- [0095] In some aspects, the compositions of the disclosure can be provided as non-effervescent or effervescent, granules and powders, to be reconstituted into a liquid dosage form. Pharmaceutically acceptable carriers and excipients used in the non-effervescent granules or powders can include, but are not limited to, diluents, sweeteners, wetting agents, and mixtures thereof. Pharmaceutically acceptable carriers and excipients used in the effervescent granules or powders can include, but are not limited to, organic acids, a source of carbon dioxide, and mixtures thereof.
- [0096] Coloring and flavoring agents can be used in all of the above dosage forms. In addition, flavoring and sweetening agents can be especially useful in the formation of chewable tablets and lozenges.
- [0097] In certain aspects, the compositions of the disclosure can be formulated as immediate or modified release dosage forms, including delayed-, extended, pulsed-, controlled, targeted-, and programmed-release forms.
- [0098] The compositions of the disclosure can comprise another active ingredient that does not impair the composition's therapeutic or prophylactic efficacy and/or can comprise a substance that augments or supplements the composition's efficacy.

- [0099] In certain aspects, a LPA1 antagonist, or the pharmaceutically acceptable salt thereof, can be administered orally. In some aspects, a LPA1 antagonist, or the pharmaceutically acceptable salt thereof, can be administered in a capsule. In some aspects, a LPA1 antagonist, or the pharmaceutically acceptable salt thereof, can be administered in a tablet.
- [0100] Compound A is typically administered in an admixture with suitable pharmaceutical diluents, excipients, or carriers (collectively referred to herein as pharmaceutical carriers) suitably selected with respect to the intended form of administration, that is, oral tablets, capsules, elixirs, syrups and the like, and consistent with conventional pharmaceutical practices.
- [0101] For instance, for oral administration in the form of a tablet or capsule, the active drug component can be combined with an oral, non-toxic, pharmaceutically acceptable, inert carrier such as lactose, sucrose, dextrose, dextrans, glucose, maltodextrin, mannitol, xylitol, sorbitol, cyclodextrins, calcium phosphate, calcium sulfate, starches, modified starches, methyl cellulose, microcrystalline cellulose, microcellulose, talc and the like; for oral administration in liquid form, the oral drug components can be combined with any oral, non-toxic, pharmaceutically acceptable inert carrier such as ethanol, glycerol, water, and the like. Moreover, when desired or necessary, suitable binders, lubricants, disintegrating agents, glidants, flavoring agents, and coloring agents can also be incorporated into the mixture.
- [0102] In still other aspects, using standard coating procedures, such as those described in Remington's Pharmaceutical Sciences, 20th Edition (2000), a film coating is provided around the formulation of Compound A.
- [0103] Dosage forms (pharmaceutical compositions) suitable for administration can contain from about 1 milligram to about 300 milligrams of active ingredient per dosage unit. In these pharmaceutical compositions the active ingredient will ordinarily be present in an amount of about 0.5-95% by weight based on the total weight of the composition. In some aspects, dosage forms suitable for administration can contain from about 10 to about 240 milligrams of active ingredient per dosage unit. In some aspects, dosage forms suitable for administration can contain from about 10, about 20, about 30, about 40, about 50, about 60, about 70, about 80, about 90, about 100, about 110, about 120, about 130, about 140, about 150, about 160, about 170, about 180, about 190, about

200, about 210, about 220, about 230, or about 240 mg of active ingredient per dosage unit, or an equivalent amount of a pharmaceutically acceptable salt thereof.

[0104] In some aspects, the present disclosure provides pharmaceutical compositions which comprise Compound A as described herein, and at least one pharmaceutical acceptable carrier.

[0105] In some aspects, the present disclosure provides a pharmaceutical formulation for oral administration comprising:

- (a) about 5 wt % to 40 wt% of Compound A;
- (b) about 30 wt % to about 90 wt % of a diluent or a mixture of diluents;
- (c) about 0 wt % to about 2 wt % of a glidant;
- (d) about 2 wt % to about 10 wt % of a disintegrating agent; and
- (e) about 0.25 wt % to about 4 wt % of a lubricant.

[0106] In some aspects, the Compound A of the pharmaceutical formulation comprises crystalline Form A. In some aspects, the pharmaceutical formulation for oral administration is a tablet.

[0107] In some aspects, the present disclosure provides a pharmaceutical formulation for oral administration comprising:

- (a) about 10 wt % to 30 wt% of Compound A;
- (b) about 40 wt % to about 85 wt % of a diluent or a mixture of diluents;
- (c) about 0 wt % to about 2 wt % of a glidant;
- (d) about 2 wt % to about 10 wt % of a disintegrating agent; and
- (e) about 0.25 wt % to about 4 wt % of a lubricant.

[0108] In some aspects, the Compound A of the pharmaceutical formulation comprises crystalline Form A. In some aspects, the pharmaceutical formulation for oral administration is a tablet.

[0109] In some aspects, the diluents described herein are selected from lactose, sucrose, dextrose, dextrates, glucose, maltodextrin, mannitol, xylitol, sorbitol, cyclodextrins, calcium phosphate, calcium sulfate, starches, modified starches, methyl cellulose, microcrystalline cellulose, microcellulose, talc, and combinations thereof. In some aspects, the diluent or diluent mixture is selected from microcrystalline cellulose and anhydrous lactose.

- [0110] As used herein, the term “glidant” refers a substance that, when added to a powder, improves the flowability of the powder, such as by reducing inter-particle friction. In some aspects, the glidant described herein is selected from silicas, silicon dioxide, CAB-0-SILM-SP, AEROSIL, talc, starch, magnesium aluminum silicates, and combinations thereof. In some aspects, the glidant is silicon dioxide.
- [0111] In some aspects, the disintegrating agent described herein is selected from natural starch, a pregelatinized starch, a sodium starch, methyl crystalline cellulose, methylcellulose, croscarmellose, croscarmellose sodium, cross-linked sodium carboxymethylcellulose, cross-linked carboxymethylcellulose, cross-linked croscarmellose, cross-linked starch such as sodium starch glycolate, cross-linked polymer such as crospovidone, cross-linked polyvinylpyrrolidone, sodium alginate, a clay, a gum, and combinations thereof. In some aspects, the disintegrating agent is croscarmellose sodium.
- [0112] In some aspects, the surfactant described herein is selected from sodium lauryl sulfate, sorbitan monooleate, polyoxyethylene sorbitan monooleate, polysorbates, polaxomers, bile salts, glyceryl monostearate, copolymers of ethylene oxide, propylene oxide, and combinations thereof. In some aspects, the surfactant is sodium lauryl sulfate.
- [0113] In some aspects, the lubricant described herein is selected from stearic acid, calcium hydroxide, talc, corn starch, sodium stearyl fumarate, stearic acid, sodium oleate, sodium stearate, sodium benzoate, sodium acetate, sodium chloride, magnesium stearate, zinc stearate, waxes, and combinations hereof. . In some aspects, the lubricant is magnesium stearate.
- [0114] In some aspects, provided herein is a pharmaceutical formulation for oral administration comprising:
- (a) about 5 wt % to 40 wt% of Compound A;
 - (b) about 15 wt % to about 70 wt % of microcrystalline cellulose and about 15 wt % to about 70 wt % of anhydrous lactose;
 - (c) about 0 wt % to about 2 wt % of silicon dioxide;
 - (d) about 2 wt % to about 6 wt % of croscarmellose sodium; and
 - (e) about 0.25 wt % to about 1.5 wt % of magnesium stearate.

[0115] In some aspects, the Compound A of the pharmaceutical formulation comprises crystalline Form A. In some aspects, the pharmaceutical formulation for oral administration is a tablet.

[0116] In some aspects, provided herein is a pharmaceutical formulation for oral administration comprising:

- (a) about 10 wt % to 30 wt% of Compound A;
- (b) about 25 wt % to about 70 wt % of microcrystalline cellulose and about 25 wt % to about 70 wt % of anhydrous lactose;
- (c) about 0 wt % to about 2 wt % of silicon dioxide;
- (d) about 2 wt % to about 6 wt % of croscarmellose sodium; and
- (e) about 0.25 wt % to about 1.5 wt % of magnesium stearate.

[0117] In some aspects, the Compound A of the pharmaceutical formulation comprises crystalline Form A. In some aspects, the pharmaceutical formulation for oral administration is a tablet. In some aspects, tablets can be prepared with the components provided in Tables 1 and/or 2.

Table 1

Components of Tablet Formulation	
Ingredient	Range
Compound A	5% to 40%
Microcrystalline cellulose	15% to 70%
Anhydrous Lactose	15% to 70%
Silicon dioxide	0% to 2%
Croscarmellose sodium	2% to 6%
Magnesium Stearate	0.25% to 1.5%
Total	Tablet weight range: 100 mg to 850 mg

Table 2

Components of Tablet Formulation	
Ingredient	Range
Compound A	10% to 30%

Microcrystalline cellulose	25% to 70%
Anhydrous Lactose	25% to 70%
Silicon dioxide	0% to 2%
Croscarmellose sodium	2% to 6%
Magnesium Stearate	0.25% to 1.5%
Total	Tablet weight range: 100 mg to 850 mg

[0118] In some aspects, the pharmaceutical compositions for oral administration can be prepared by direct compression or granulation (dry, wet, or melt granulation).

IV. *Methods of Treatment*

[0119] The present disclosure provides methods of treating interstitial lung disease by administering Compound A, an LPA₁ antagonist. Lysophospholipids are membrane-derived bioactive lipid mediators. Lysophospholipids include, but are not limited to, lysophosphatidic acid (1-acyl-2-hydroxy-*sn*-glycero-3-phosphate; LPA), sphingosine 1-phosphate (S1P), lysophosphatidylcholine (LPC), and sphingosylphosphorylcholine (SPC). Lysophospholipids affect fundamental cellular functions that include cellular proliferation, differentiation, survival, migration, adhesion, invasion, and morphogenesis. These functions influence many biological processes that include neurogenesis, angiogenesis, wound healing, immunity, and carcinogenesis.

[0120] LPA acts through sets of specific G protein-coupled receptors (GPCRs) in an autocrine and paracrine fashion. LPA binding to its cognate GPCRs (LPA₁, LPA₂, LPA₃, LPA₄, LPA₅, LPA₆) activates intracellular signaling pathways to produce a variety of biological responses.

[0121] Lysophospholipids, such as LPA, are quantitatively minor lipid species compared to their major phospholipid counterparts (*e.g.*, phosphatidylcholine, phosphatidylethanolamine, and sphingomyelin). LPA has a role as a biological effector molecule, and has a diverse range of physiological actions such as, but not limited to, effects on blood pressure, platelet activation, and smooth muscle contraction, and a variety of cellular effects, which include cell growth, cell rounding, neurite retraction, and actin stress fiber formation and cell migration. The effects of LPA are predominantly receptor mediated.

[0122] Activation of the LPA receptors (LPA₁, LPA₂, LPA₃, LPA₄, LPA₅, LPA₆) with LPA mediates a range of downstream signaling cascades. These include, but are not limited to, mitogen-activated protein kinase (MAPK) activation, adenylyl cyclase (AC) inhibition/activation, phospholipase C (PLC) activation/Ca²⁺ mobilization, arachidonic acid release, Akt/PKB activation, and the activation of small GTPases, Rho, ROCK, Rac, and Ras. Other pathways that are affected by LPA receptor activation include, but are not limited to, cyclic adenosine monophosphate (cAMP), cell division cycle 42/GTP-binding protein (Cdc42), proto-oncogene serine/threonine-protein kinase Raf (c-RAF), proto-oncogene tyrosine-protein kinase Src (c-src), extracellular signal-regulated kinase (ERK), focal adhesion kinase (FAK), guanine nucleotide exchange factor (GEF), glycogen synthase kinase 3b (GSK3b), c-jun amino-terminal kinase (JNK), MEK, myosin light chain II (MLC II), nuclear factor kB (NF-kB), N-methyl-D-aspartate (NMDA) receptor activation, phosphatidylinositol 3-kinase (PI3K), protein kinase A (PKA), protein kinase C (PKC), ras-related C3 botulinum toxin substrate 1 (RAC1). The actual pathway and realized end point are dependent on a range of variables that include receptor usage, cell type, expression level of a receptor or signaling protein, and LPA concentration. Nearly all mammalian cells, tissues and organs co-express several LPA-receptor subtypes, which indicates that LPA receptors signal in a cooperative manner. LPA₁, LPA₂, and LPA₃ share high amino acid sequence similarity.

[0123] LPA is produced from activated platelets, activated adipocytes, neuronal cells, and other cell types. Serum LPA is produced by multiple enzymatic pathways that involve monoacylglycerol kinase, phospholipase A₁, secretory phospholipase A₂, and lysophospholipase D (lysoPLD), including autotaxin. Several enzymes are involved in LPA degradation: lysophospholipase, lipid phosphate phosphatase, and LPA acyl transferase such as endophilin. LPA concentrations in human serum are estimated to be 1–5 µM. Serum LPA is bound to albumin, low-density lipoproteins, or other proteins, which possibly protect LPA from rapid degradation. LPA molecular species with different acyl chain lengths and saturation are naturally occurring, including 1-palmitoyl (16:0), 1-palmitoleoyl (16:1), 1-stearoyl (18:0), 1-oleoyl (18:1), 1-linoleoyl (18:2), and 1-arachidonyl (20:4) LPA. Quantitatively minor alkyl LPA has biological activities similar to acyl LPA, and different LPA species activate LPA receptor subtypes with varied efficacies.

- [0124] LPA₁ (previously called VZG-1/EDG-2/mrec1.3) couples with three types of G proteins, G_{i/o}, G_q, and G_{12/13}. Through activation of these G proteins, LPA induces a range of cellular responses through LPA₁ including but not limited to: cell proliferation, serum-response element (SRE) activation, mitogen-activated protein kinase (MAPK) activation, adenylyl cyclase (AC) inhibition, phospholipase C (PLC) activation, Ca²⁺ mobilization, Akt activation, and Rho activation.
- [0125] Wide expression of LPA₁ is observed in adult mice, with clear presence in testis, brain, heart, lung, small intestine, stomach, spleen, thymus, and skeletal muscle. Similarly, human tissues also express LPA₁; it is present in brain, heart, lung, placenta, colon, small intestine, prostate, testis, ovary, pancreas, spleen, kidney, skeletal muscle, and thymus.
- [0126] The term "LPA-dependent", as used herein, refers to conditions or disorders that would not occur, or would not occur to the same extent, in the absence of LPA.
- [0127] The term "LPA-mediated," as used herein, refers to conditions or disorders that might occur in the absence of LPA but can occur in the presence of LPA.
- [0128] The terms "fibrosis" and "fibrotic disease," as used herein, refer to conditions that are associated with the abnormal accumulation of cells and/or fibronectin and/or collagen and/or increased fibroblast recruitment and include but are not limited to fibrosis of individual organs or tissues such as the heart, kidney, liver, joints, lung, pleural tissue, peritoneal tissue, skin, cornea, retina, musculoskeletal and digestive tract, such as idiopathic pulmonary fibrosis, scleroderma, and chronic nephropathies.
- [0129] Exemplary diseases, disorders, or conditions that involve fibrosis include, but are not limited to: lung diseases associated with fibrosis, *e.g.*, 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 disease (COPD), 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); chronic nephropathies associated with injury/fibrosis (kidney fibrosis), *e.g.*, glomerulonephritis secondary to systemic inflammatory diseases such as lupus and scleroderma, diabetes, glomerular nephritis, focal segmental glomerular sclerosis, IgA nephropathy,

hypertension, allograft and Alport; gut fibrosis, *e.g.*, scleroderma, and radiation induced gut fibrosis; liver fibrosis, *e.g.*, cirrhosis, alcohol induced liver fibrosis, nonalcoholic steatohepatitis (NASH), biliary duct injury, primary biliary cirrhosis, infection or viral induced liver fibrosis (*e.g.*, chronic HCV infection), and autoimmune hepatitis; head and neck fibrosis, *e.g.*, radiation induced; corneal scarring, *e.g.*, LASIK (laser-assisted in situ keratomileusis), corneal transplant, and trabeculectomy; hypertrophic scarring and keloids, *e.g.*, burn induced or surgical; and other fibrotic diseases, *e.g.*, sarcoidosis, scleroderma, spinal cord injury/fibrosis, myelofibrosis, vascular restenosis, atherosclerosis, arteriosclerosis, Wegener's granulomatosis, mixed connective tissue disease, and Peyronie's disease.

[0130] Other diseases, disorders, or conditions where LPA₁ receptors can be involved include atherosclerosis, thrombosis, heart disease, vasculitis, formation of scar tissue, restenosis, phlebitis, COPD (chronic obstructive pulmonary disease), pulmonary hypertension, pulmonary fibrosis, pulmonary inflammation, bowel adhesions, bladder fibrosis and cystitis, fibrosis of the nasal passages, sinusitis, inflammation mediated by neutrophils, and fibrosis mediated by fibroblasts, dermatological disorders including proliferative or inflammatory disorders of the skin such as, atopic dermatitis, bullous disorders, collagenosis, psoriasis, psoriatic lesions, dermatitis, contact dermatitis, eczema, rosacea, wound healing, scarring, hypertrophic scarring, keloids, Kawasaki Disease, rosacea, Sjögren-Larsson Syndrome, and urticaria, respiratory diseases including asthma, adult respiratory distress syndrome and allergic (extrinsic) asthma, non-allergic (intrinsic) asthma, acute severe asthma, chronic asthma, clinical asthma, nocturnal asthma, allergen-induced asthma, aspirin-sensitive asthma, exercise-induced asthma, isocapnic hyperventilation, child-onset asthma, adult-onset asthma, cough-variant asthma, occupational asthma, steroid-resistant asthma, seasonal asthma, seasonal allergic rhinitis, perennial allergic rhinitis, chronic obstructive pulmonary disease, including chronic bronchitis or emphysema, pulmonary hypertension, interstitial lung fibrosis and/or airway inflammation and cystic fibrosis, and hypoxia, and inflammatory/immune disorders including psoriasis, rheumatoid arthritis, vasculitis, inflammatory bowel disease, dermatitis, osteoarthritis, asthma, inflammatory muscle disease, allergic rhinitis, vaginitis, interstitial cystitis, scleroderma, eczema, allogeneic or xenogeneic transplantation (organ, bone marrow, stem cells and other cells and tissues) graft rejection, graft-versus-host

disease, lupus erythematosus, inflammatory disease, type I diabetes, pulmonary fibrosis, dermatomyositis, Sjögren's syndrome, thyroiditis (*e.g.*, Hashimoto's and autoimmune thyroiditis), myasthenia gravis, autoimmune hemolytic anemia, multiple sclerosis, cystic fibrosis, chronic relapsing hepatitis, primary biliary cirrhosis, allergic conjunctivitis and atopic dermatitis.

[0131] In certain aspects, the present disclosure provides a method of treating interstitial lung disease in a subject in need thereof, the method comprising administering an LPA₁ antagonist to the subject at one or more daily dosages lower than the LPA₁ antagonist's standard daily dosage during a dose titration period of treatment, then increasing the daily dosage to the standard daily dosage of the LPA₁ antagonist. In some aspects, the term "dose titration period of treatment" refers to the period of time where the LPA₁ antagonist is administered at one or more daily dosages that are below the LPA₁ antagonist's standard daily dosage. In certain aspects, the dose titration period of treatment is completed within a specified number of days. In certain aspects, and as used herein, "the dose titration period of treatment is completed within X days," where X is an integer, means the subject is administered an LPA₁ antagonist on Day 1 of the dose titration period at a daily dosage below the LPA₁ antagonist's standard daily dosage, and is administered the standard daily dosage of the LPA₁ antagonist on or before Day X + 1. For example, if the dose titration period of treatment recited as being completed within 21 days, the subject will be administered an LPA₁ antagonist on Day 1 of the dose titration period of treatment at a daily dosage below the LPA₁ antagonist's standard daily dosage, and on or before Day 22 will be administered the LPA₁ antagonist's standard daily dosage.

[0132] In certain aspects of the present disclosure, the dose titration period of treatment is completed within 21 days. In some aspects, the dose titration period of treatment is completed within 14 days. In some aspects, the dose titration period of treatment is completed within 10 days. In some aspects, the dose titration period of treatment is completed within 7 days. In some aspects, the dose titration period of treatment is completed within 5 days. In some aspects, the dose titration period of treatment is completed within 21, 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, or 5 days.

[0133] In certain aspects, the methods described herein comprise an initial period of treatment. In some aspects, the dose titration period of treatment described herein

comprises an initial period of treatment, where the subject is administered a first daily dosage of an LPA₁ antagonist that is below the LPA₁ antagonist's standard daily dosage. In certain aspects, the initial period of treatment is completed within a specified number of days. In certain aspects, and as used herein, "the initial period of treatment is completed within X days," where X is an integer, means the subject is administered an LPA₁ antagonist on Day 1 of the initial period of treatment at a daily dosage below the LPA₁ antagonist's standard daily dosage, and is administered a daily dosage of the LPA₁ antagonist that is below the LPA₁ antagonist's standard daily dosage but higher than the daily dosage administered during the initial period of treatment on or before Day X + 1. For example, if the initial period of treatment is recited as being completed within 7 days, the subject will be administered an LPA₁ antagonist on Day 1 of the initial period of treatment at a daily dosage below the LPA₁ antagonist's standard daily dosage, and on or before Day 7 will be administered the LPA₁ antagonist at a daily dosage that is lower than the LPA₁ antagonist's standard daily dosage but higher than the daily dosage administered during the initial period.

[0134] In some aspects, the initial period of treatment is completed within 7 days. In some aspects, the initial period of treatment is completed within 4 days. In some aspects, the initial period of treatment is completed within 3 days. In some aspects, the initial period of treatment is completed within 2 days. In some aspects, the initial period of treatment is completed within 1 day. In some aspects, the initial period of treatment is completed within 7, 6, 5, 4, 3, 2, or 1 days.

[0135] In certain aspects, the methods described herein comprise a second period of treatment. In some aspects, the dose titration period of treatment comprises a second period of treatment, where the subject is administered a daily dosage of the LPA₁ antagonist that is below the LPA₁ antagonist's standard daily dosage but higher than the daily dosage administered during the initial period of treatment. In certain aspects, the second period of treatment is completed within a specified number of days. In certain aspects, and as used herein, "the second period of treatment is completed within X days," where X is an integer, means the subject is administered an LPA₁ antagonist on Day 1 of the second period treatment at a daily dosage higher than the daily dosage administered during the initial period of treatment but below the LPA₁ antagonist's standard daily dosage, and is administered a daily dosage of the LPA₁ antagonist that is higher than the

daily dosage administered during the second period of treatment on or before Day $X + 1$. For example, if the second period of treatment is recited as being completed within 7 days, the subject will be administered an LPA₁ antagonist on Day 1 at a daily dosage higher than the daily dosage administered during the initial period of treatment but below the LPA₁ antagonist's standard daily dosage, and on or before Day 7 will be administered the LPA₁ antagonist at a daily dosage that is higher than the daily dosage administered during the second period.

[0136] In some aspects, the second period of treatment is completed within 7 days. In some aspects, the second period of treatment is completed within 4 days. In some aspects, the second period of treatment is completed within 3 days. In some aspects, the second period of treatment is completed within 2 days. In some aspects, the second period of treatment is completed within 1 day. In some aspects, the second period of treatment is completed within 7, 6, 5, 4, 3, 2, or 1 days.

[0137] In some aspects, the dose titration period of treatment comprises a third period of treatment, where the subject is administered a daily dosage of the LPA₁ antagonist that is below the LPA₁ antagonist's standard daily dosage but higher than the daily dosage administered during the second period of treatment. In certain aspects, the third period of treatment is completed within a specified number of days. In certain aspects, and as used herein, "the third period of treatment is completed within X days," where X is an integer, means the subject is administered an LPA₁ antagonist on Day 1 of the third period treatment at a daily dosage higher than the daily dosage administered during the second period of treatment but below the LPA₁ antagonist's standard daily dosage, and is administered a daily dosage of the LPA₁ antagonist that is higher than the daily dosage administered during the third period of treatment on or before Day $X + 1$. For example, if the third period of treatment is recited as being completed within 7 days, the subject will be administered an LPA₁ antagonist on Day 1 of the third period of treatment at a daily dosage higher than the daily dosage administered during the second period of treatment but below the LPA₁ antagonist's standard daily dosage, and on or before Day 7 will be administered the LPA₁ antagonist at a daily dosage that is higher than the daily dosage administered during the third period.

[0138] In some aspects, the third period of treatment is completed within 7 days. In some aspects, the third period of treatment is completed within 4 days. In some aspects, the

third period of treatment is completed within 3 days. In some aspects, the third period of treatment is completed within 2 days. In some aspects, the third period of treatment is completed within 1 day. In some aspects, the third period of treatment is completed within 7, 6, 5, 4, 3, 2, or 1 days.

[0139] In some aspects, the dose titration period of treatment comprises a fourth period of treatment, where the subject is administered a daily dosage of the LPA₁ antagonist that is below the LPA₁ antagonist's standard daily dosage but higher than the daily dosage administered during the third period of treatment. In certain aspects, the fourth period of treatment is completed within a specified number of days. In certain aspects, and as used herein, "the fourth period of treatment is completed within X days," where X is an integer, means the subject is administered an LPA₁ antagonist on Day 1 of the fourth period treatment at a daily dosage higher than the daily dosage administered during the third period of treatment but below the LPA₁ antagonist's standard daily dosage, and is administered a daily dosage of the LPA₁ antagonist that is higher than the daily dosage administered during the fourth period of treatment on or before Day X + 1. For example, if the fourth period of treatment is recited as being completed within 7 days, the subject will be administered an LPA₁ antagonist on Day 1 of the fourth period of treatment at a daily dosage higher than the daily dosage administered during the third period of treatment but below the LPA₁ antagonist's standard daily dosage, and on or before Day 7 will be administered the LPA₁ antagonist at a daily dosage that is higher than the daily dosage administered during the fourth period.

[0140] In some aspects, the fourth period of treatment within the dose titration period is completed within 7 days. In some aspects, fourth period of treatment within the dose titration period is completed within 4 days. In some aspects, the fourth period of treatment within the dose titration period is completed within 3 days. In some aspects, the fourth period of treatment within the dose titration period is completed within 2 days. In some aspects, the fourth period of treatment within the dose titration period is completed within 1 day. In some aspects, the fourth period of treatment within the dose titration period is completed within 7, 6, 5, 4, 3, 2, or 1 days.

[0141] In some aspects, the dose titration period of treatment comprises a fifth period of treatment, where the subject is administered a daily dosage of the LPA₁ antagonist that is below the LPA₁ antagonist's standard daily dosage but higher than the daily dosage

administered during the fourth period of treatment. In certain aspects, the fifth period of treatment is completed within a specified number of days. In certain aspects, and as used herein, “the fifth period of treatment is completed within X days,” where X is an integer, means the subject is administered an LPA₁ antagonist on Day 1 of the fifth period treatment at a daily dosage higher than the daily dosage administered during the fourth period of treatment but below the LPA₁ antagonist’s standard daily dosage, and is administered a daily dosage of the LPA₁ antagonist that is higher than the daily dosage administered during the fifth period of treatment on or before Day X + 1. For example, if the fifth period of treatment is recited as being completed within 7 days, the subject will be administered an LPA₁ antagonist on Day 1 of the fifth period of treatment at a daily dosage higher than the daily dosage administered during the fourth period of treatment but below the LPA₁ antagonist’s standard daily dosage, and on or before Day 7 will be administered the LPA₁ antagonist at a daily dosage that is higher than the daily dosage administered during the fifth period.

[0142] In some aspects, the fifth period of treatment is completed within 7 days. In some aspects, the fifth period of treatment is completed within 4 days. In some aspects, the fifth period of treatment is completed within 3 days. In some aspects, the fifth period of treatment is completed within 2 days. In some aspects, the fifth period of treatment is completed within 1 day. In some aspects, the fifth period of treatment is completed within 7, 6, 5, 4, 3, 2, or 1 days.

[0143] Currently there are two approved treatments for interstitial lung disease: nintedanib and perfenidone, though several compounds are currently in development. In certain aspects of the present disclosure, the subject being administered the LPA₁ antagonist is receiving concomitant treatment with one or more therapies for interstitial lung disease. In some aspects, the one or more therapies is selected from nintedanib and perfenidone.

[0144] In some aspects, the subject is administered the LPA₁ antagonist with food. In some aspects, the subject is administered the LPA₁ antagonist without food.

[0145] In some aspects, the subject administered the LPA₁ antagonist experiences a slower disease progression than an untreated subject. In some aspects, disease progression is measured by the subject’s decrease in forced vital capacity (FVC). In some aspects, the subject treated with the LPA₁ antagonist experiences a smaller decline in forced vital

capacity (FVC) after a treatment period compared to an untreated subject. FVC is the amount of air that a subject is able to forcibly exhale from his / her lungs after taking the deepest breath they can. FVC is typically measured using spirometry testing, which involves placing a special mask over the subject's face and having the subject inhale and exhale as forcibly as they can, while the measurements are collected. The assessment is typically performed according to the manual provided by the central vendor. In some aspects, the subject is seated in a chair and asked to breathe comfortably, a clip is placed over the subject's nose, the subject seals their lips tightly over the spirometer tube, inhales as deeply as possible, and exhales into the spirometer tube as forcefully as possible. In some aspects, the spirometry test is performed prior to the morning dose, approximately the same time (+/- 2 hours) at every visit in which spirometry is performed.

[0146] In some aspects, disease progression is measured by the subject's diffusing capacity of carbon monoxide (DLCO). DLCO is a measurement of the extent to which oxygen passes from the alveoli into the blood. The test typically involves measuring the partial pressure difference between inspired and expired carbon monoxide and relies on the strong affinity and large absorption capacity of red blood cells for carbon monoxide, thus demonstrating gas uptake by the capillaries that are less dependent on cardiac output.

[0147] Generally, the single-breath diffusing capacity test is the most common way to determine DLCO. Typically, the test is performed by having the subject blow out all of the air that they can, leaving only the residual lung volume of air. The subject then inhales a test gas mixture rapidly and completely, reaching the total lung capacity as nearly as possible. The test gas mixture typically contains a small amount of carbon monoxide (usually 0.3%) and a tracer gas (helium or methane) that is freely distributed throughout the alveolar space, but which does not cross the alveolar-capillary membrane. The test gas is held in the lung for about 10 seconds during which time the carbon monoxide (but not the tracer gas) continuously moves from the alveoli into the blood. The subject then exhales into the analyzer tube. By analyzing the concentrations of carbon monoxide and inert gas in the inspired gas and in the exhaled gas, it is possible to calculate single-breath diffusing capacity of the lung for carbon monoxide (DLCO SB).

[0148] In some aspects, disease progression can be measured by High-resolution Computed Tomography (HRCT). IPF is a specific form of chronic, progressive fibrotic interstitial pneumonia of unknown cause, limited to the lungs and associated with the

histopathologic and/or radiologic pattern of UIP. The hallmark pathologic feature of UIP is a heterogeneous, variegated appearance with alternating areas of healthy lung, interstitial inflammation, fibrosis, and honeycomb change, while fibrosis predominates over inflammation. The characteristic HRCT manifestations of IPF consist of symmetric bilateral reticulation, architectural distortion, and honeycombing involving mainly the subpleural lung regions and lower lobes. As IPF progresses, honeycombing becomes more prominent.

[0149] Although identification of UIP on surgical lung biopsy has been used for diagnosis, typical clinical and HRCT features may suffice for a confident diagnosis and eliminate the need for surgical lung biopsy. Accordingly, HRCT assessment has been adopted as an important diagnostic criterion in the 2018 ATS/ERS/JRS/ALAT Clinical Practice Guidelines. Extent of reticulation and honeycombing on HRCT findings is considered an important independent predictor of mortality in patients with IPF. HRCT has been applied in multiple clinical studies of lung fibrosis for drug development, serving as an inclusion criterion, a predictive marker of positive treatment response, and efficacy readout.

[0150] A computer-assisted diagnosis (CAD) score to quantify lung fibrosis as the percentage involvement of reticulation patterns based on texture measures from HRCT has been developed and validated as a measure of quantitative lung fibrosis (QLF) and a potential surrogate imaging marker. Computer-assisted diagnosis scores of QLF have been successfully applied as outcome measurements to test treatment efficacy in an ILD trial. Compared with visual assessments, CAD scores have been shown to improve objectivity, sensitivity, and repeatability when measuring quantitative changes in lung features.

[0151] In some aspects, HRCT can be performed on study participants during the screening period, at Week 52, and annually thereafter in the Phase 3 studies described herein. To ensure comparability, the same scan, equipment, method, and technique used during the baseline HRCT scan can be used for the follow-up HRCT scan (Week 52). In some aspects, screening HRCT scans can be performed at total lung capacity and residual volume, with no contrast agent administration, reconstructed every 1 to 1.5 mm, using a low-dose protocol. In some aspects, at Week 52, and annually thereafter, HRCT can be performed at total lung capacity. Residual volume HRCT is optional at Week 52, and

annually thereafter. For efficacy assessments, HRCT images of both during the screening period and follow-up scans (Week 52) can be analyzed by a centralized blinded reader.

[0152] The HRCT analysis focuses on visual and CAD scores for regional lung fibrosis evaluation. Changes in the lung fibrosis scores from the screening period HRCT are used to evaluate the treatment responses. In some aspects, the correlation of HRCT data to other efficacy readouts and biomarker data can be performed if applicable.

[0153] In some aspects, disease progression can be measured by the time it takes a subject to experience a disease progression event. In some aspects, the subject administered the LPA₁ antagonist experiences a greater time to first disease progression event after a treatment period than an untreated subject. In some aspects, the first disease progression event is absolute percentage predicted forced vital capacity (ppFVC) of $\geq 10\%$ from baseline. An absolute or relative decline in % predicted FVC $\geq 10\%$ is associated with mortality. In some aspects, the subject treated with Compound A experiences a greater time to absolute percentage predicted forced vital capacity (ppFVC) of $\geq 10\%$ from baseline than an untreated subject.

[0154] In some aspects, the first disease progression event is acute exacerbation (e.g., sudden worsening) of his/her lung fibrosis. In some aspects, the subject treated with Compound A experiences a greater time to acute exacerbation of lung fibrosis than an untreated subject.

[0155] In some aspects, the first disease progression event is respiratory hospitalization. In some aspects, the subject treated with Compound A experiences a greater time to respiratory hospitalization than an untreated subject.

[0156] In some aspects, the first disease progression event is lung fibrosis-related hospitalization. In some aspects, the subject treated with Compound A, or a pharmaceutically acceptable salt thereof, experiences a greater time to lung fibrosis-related hospitalization than an untreated subject.

[0157] In some aspects, the first disease progression event is lung transplantation. In some aspects, the subject treated with the LPA₁ antagonist experiences a greater time to lung transplantation than an untreated subject.

[0158] In some aspects, the first disease progression event is mortality. In some aspects, the subject treated with the LPA₁ antagonist experiences a greater time to all-cause mortality than an untreated subject.

- [0159] In some aspects, the subject experiences a greater time to first disease progression event after a treatment period than an untreated subject, wherein the first disease progression event is selected from:
- absolute percentage predicted forced vital capacity (ppFVC) of $\geq 10\%$ from baseline;
 - acute exacerbation of lung fibrosis;
 - respiratory hospitalization;
 - lung transplantation; and
 - all-cause mortality.
- [0160] In some aspects, the subject experiences a greater time to first disease progression event after a treatment period than an untreated subject, wherein the first disease progression event is selected from:
- absolute predicted forced vital capacity (ppFVC) decline of $\geq 10\%$ from baseline;
 - acute exacerbation of lung fibrosis;
 - lung fibrosis-related hospitalization; and
 - all-cause mortality.
- [0161] In some aspects, subjects of the Phase 3 trials described herein can be asked to complete Clinical Outcomes Assessments (COA) measures, including the Living with Pulmonary Fibrosis Questionnaire (L-PF), EQ-5D-5L, and perform the 6-minute walk test (6MWT) at the Day 1 (baseline), Week 28, and Week 52 visits. The Living with Pulmonary Fibrosis (L-PF) questionnaire assesses symptoms and quality of life in patients with fibrosing interstitial lung diseases (ILDs). Its Dyspnoea and Cough domains, whose items' responses are based on a 24-hour recall, have scores ranging from 0 to 100, with higher scores indicating greater symptom severity (see, for example, Swigris JJ, *et al. BMJ Open Resp Res* 2022;9:e001167. doi:10.1136/bmjresp-2021-001167). In some aspects, disease progression can be measured by a change in score in the Living with Pulmonary Fibrosis (L-PF) questionnaire.
- [0162] The EQ-5D-5L is a standardized instrument used to measure self-reports of general health status. The instrument has two components, a descriptive system, and a visual analogue scale (VAS). The descriptive system consists of five dimensions: Mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has five levels, reflecting no problems, slight problems, moderate problems,

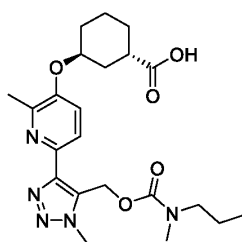
severe problems, and extreme problems. A dimension for which there are no problems is said to be at level 1, while a dimension for which there are extreme problems is said to be at level 5. Thus, the vectors 11111 and 55555 represent the best health state and the worst health state, respectively. Altogether, the instrument describes 3,125 different health states. Empirically-derived weights can be applied to an individual's responses to the EQ-5D-5L descriptive system to generate a utility index using a flexible, copula-based model developed by Hernandez-Alava and Pudney that is a system of ordinal regressions with a flexible copula-mixture residual distribution, or the one recommended by National Institute for Health and Care Excellence at the time of data analysis. Value sets have been derived for the EQ-5D-5L in the United Kingdom, United States, France, Germany, Spain, Europe, and several other countries. The EQ-5D-5L VAS allows participants to rate their own current health on a 0- to 100-point scale ranging from "the worst health you can imagine" to the "best health you can imagine," respectively. The minimal important difference is a 7-point change in score for the EQ-5D-5L VAS and 0.08 for utility index will be used as recommended in the literature for within-group, within-person, and between-group differences. The EQ-5D-5L uses a recall period of "today."

[0163] The 6MWT is a submaximal exercise test used to assess aerobic capacity and endurance. Before starting the test, the participant should be informed that the objective is to walk as far as possible during 6 minutes. The test should be conducted on a hard, flat surface, such as located in a hallway. If the participant becomes breathless or exhausted, then he or she may slow down, stop, or rest, as necessary. The participant may lean against a wall or use mobility aids while resting but should resume walking as soon as able to do so. He or she should be informed of the time remaining after each minute elapses and 15 seconds prior to the test's conclusion. At the end of 6 minutes, the participant should be told to stop, and the distance traveled should be measured and recorded in the eCRF. In patients with IPF, the threshold for clinically meaningful change in 6MWT outcomes has been estimated to range from 24 to 45 meters and more recently, 21.7 meters for patients with IPF. The 6MWT must be administered after the spirometry assessment, and if possible, should be administered after eCOAs. Additional details on the 6MWT assessment and related oxygen titration walk are provided in the Guidance Manual for Conducting a 6MWT.

- [0164] Electronic diary devices will be available to subjects in the Phase 3 studies described herein at screening, and subjects will be trained on the use of the eCOA device to complete the daily PRO assessments. Starting on Day -14 and on every day through Day -1, subjects will complete the L-PF cough and dyspnea daily questionnaires for a consecutive 14-day (2-week) period prior to their Day 1 visit. Subjects will also complete the patient global impression of lung fibrosis symptom severity (PGI-S) cough and dyspnea questionnaires at Day -8 and Day -1 using the eCOA device.
- [0165] At Day 1, eligible subjects will return to the site with their eCOA device. Subjects will complete L-PF fatigue and impacts domain items, Cough NRS (cough severity numeric rating scale, an 11-point scale ranging from 0 to 10), and EQ-5D-5L questionnaires on the eCOA device prior to any other procedure taking place, where possible, and prior to any meaningful discussion about the study or IMP with investigative site staff. Subjects will complete PGI-S and PGI-C assessments for shortness of breath (dyspnea), cough, and overall disease symptoms on the eCOA device the day before the Week 16, Week 28, Week 40, and Week 52 visits.
- [0166] Additionally, all subjects in the Phase 3 trials described herein will be asked to perform an oxygen titration test at screening only. The oxygen level established at screening should be used for the 6MWT test at screening, and the Week 28 and Week 52 visits. COA measures other than the 6MWT (including oxygen titration walk) will be administered electronically, and the responses entered by trial participants into source records cannot be overridden by site staff or investigators. When possible, eCOA measures should be administered using the electronic device prior to other study-related procedures and prior to any meaningful discussion about the study, or IMP, with investigative site staff. If a participant refuses to complete all or any part of a questionnaire, this will be documented. If exceptional circumstances preclude the continued administration of measures using planned modalities, then alternate administration methods may be required after consulting with the Sponsor.
- [0167] In some aspects, the subject administered Compound A experiences a smaller increase in cough domain score as measured by the Living with Pulmonary Fibrosis (L-PF) questionnaire over a treatment period than an untreated subject. In some aspects, the subject experiences a smaller increase in dyspnea score as measured by the Living with Pulmonary Fibrosis (L-PF) questionnaire over a treatment period than an untreated

subject. The L-PF is a multidimensional measure of the health-related quality of life of patients living with pulmonary fibrosis. The L-PF was adapted from the Living with Idiopathic Pulmonary Fibrosis Questionnaire (L-IPF), which was in turn developed from the prior “A Tool to Assess Quality of Life in IPF.” The L-PF is currently under review thorough the Food and Drug Administration Drug Development Tool (DDT) Qualification Process (DDT COA #000027). The L-PF was adapted from the L-IPF through the removal of the word “Idiopathic” from the L-IPF’s title and the L-IPF measure’s patient completion directions; this adaptation allows for the same questionnaire to be used in IPF and PPF patient populations to assess the symptoms and impacts of progressing fibrosis. The conceptual framework for the L-PF includes 2 modules: Symptoms and Impacts of disease. The Symptoms module consists of 3 domains: Shortness of breath (dyspnea), cough, and fatigue, which are measured using a 24-hour recall period. The Impacts module measures activities of daily living including physical and emotional well-being, sleep, and social aspects, with a 7-day recall period. Scoring is available per symptom domain and for the Impacts module ranging from 0 to 100, with higher scores indicating greater impairment. Although all domains will be administered during the course of the study, only cough and dyspnea domains are considered key secondary endpoints as those domains are most critical for patients with IPF. Validation of the psychometric properties of the L-PF is ongoing, although the instrument has been used in trials of treatments for patients with PF-ILD.

[0168] In some aspects, the LPA₁ antagonist is (1S,3S)-3-((2-methyl-6-(1-methyl-5-(((methyl(propyl)carbamoyl)oxy)methyl)-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylic acid (hereafter referred as to “Compound A”) is described in U.S. Patent Application Publication No. 2017/0360759.



Compound A

Compound A is a potent LPA₁ antagonist in vitro (LPA₁ K_b = 6.9 nM in CHO cells overexpressing human LPA₁ and LPA₁ K_b = 5.9 nM in normal human lung fibroblasts). Compound A is currently in clinical development as a therapy for IPF and PF-ILD.

[0169] In certain aspects, the standard daily dosage of Compound A is about 100 mg to about 150 mg of Compound A per day, or an equivalent amount of a pharmaceutically acceptable salt thereof. In some aspects, the standard daily dosage of Compound A is about 110 mg to about 130 mg of Compound A per day, or an equivalent amount of a pharmaceutically acceptable salt thereof. In some aspects, the standard daily dosage of Compound A is about 100, about 105, about 110, about 115, about 120, about 125, about 130, about 135, about 140, about 145, or about 150 mg of Compound A per day, or an equivalent amount of a pharmaceutically acceptable salt thereof. In some aspects, the standard daily dosage of Compound A is about 120 mg of Compound A per day, or an equivalent amount of a pharmaceutically acceptable salt thereof.

[0170] In some aspects, the subject is administered Compound A, or a pharmaceutically acceptable salt thereof, once daily. In some aspects, the subject is administered Compound A, or a pharmaceutically acceptable salt thereof, twice daily. In some aspects, the subject is administered Compound A, or a pharmaceutically acceptable salt thereof, three times daily. In some aspects, the subject is administered Compound A, or a pharmaceutically acceptable salt thereof, four times daily. In some aspects, the subject is administered Compound A, or a pharmaceutically acceptable salt thereof, five times daily.

[0171] In some aspects, the subject is administered about 10 mg/day of Compound A, or an equivalent amount of a pharmaceutically acceptable salt thereof, during the dose titration period of treatment. In some aspects, the subject is administered about 20 mg/day of Compound A, or an equivalent amount of a pharmaceutically acceptable salt thereof, during the dose titration period of treatment. In some aspects, the subject is administered about 30 mg/day of Compound A, or an equivalent amount of a pharmaceutically acceptable salt thereof, during the dose titration period of treatment. In some aspects, the subject is administered about 40 mg/day of Compound A, or an equivalent amount of a pharmaceutically acceptable salt thereof, during the dose titration period of treatment. In some aspects, the subject is administered about 50 mg/day, or an equivalent amount of a

pharmaceutically acceptable salt thereof, of Compound A during the dose titration period of treatment.

[0172] In some aspects, the dose titration period of treatment is completed within 21 days. In some aspects, the dose titration period of treatment is completed within 14 days. In some aspects, the dose titration period of treatment is completed within 10 days. In some aspects, the dose titration period of treatment is completed within 7 days. In some aspects, the dose titration period of treatment is completed within 5 days.

[0173] In some aspects, the subject is administered about 10 mg/day of Compound A, or an equivalent amount of a pharmaceutically acceptable salt thereof, during the initial period of treatment. In some aspects, the subject is administered about 20 mg/day of Compound A, or an equivalent amount of a pharmaceutically acceptable salt thereof, during the initial period of treatment. In some aspects, the subject is administered about 30 mg/day of Compound A, or an equivalent amount of a pharmaceutically acceptable salt thereof, during the initial period of treatment. In some aspects, the subject is administered about 40 mg/day of Compound A, or an equivalent amount of a pharmaceutically acceptable salt thereof, during the initial period of treatment. In some aspects, the subject is administered about 50 mg/day of Compound A, or an equivalent amount of a pharmaceutically acceptable salt thereof, during the initial period of treatment. In some aspects, the subject is administered about 60 mg/day of Compound A, or an equivalent amount of a pharmaceutically acceptable salt thereof, during the initial period of treatment. In some aspects, the subject is administered about 70 mg/day of Compound A, or an equivalent amount of a pharmaceutically acceptable salt thereof, during the initial period of treatment. In some aspects, the subject is administered about 80 mg/day of Compound A, or an equivalent amount of a pharmaceutically acceptable salt thereof, during the initial period of treatment. In some aspects, the subject is administered about 90 mg/day of Compound A, or an equivalent amount of a pharmaceutically acceptable salt thereof, during the initial period of treatment. In some aspects, the subject is administered about 100 mg/day of Compound A, or an equivalent amount of a pharmaceutically acceptable salt thereof, during the initial period of treatment. In some aspects, the subject is administered about 110 mg/day of Compound A, or an equivalent amount of a pharmaceutically acceptable salt thereof, during the initial period of treatment.

- [0174] In some aspects, the initial period of treatment is completed within 7 days. In some aspects, the initial period of treatment is completed within 4 days. In some aspects, the initial period of treatment is completed within 3 days. In some aspects, the initial period of treatment is completed within 2 days. In some aspects, the initial period of treatment is completed within 1 day.
- [0175] In some aspects, the subject is administered about 20 mg/day of Compound A, or an equivalent amount of a pharmaceutically acceptable salt thereof, during the second period of treatment. In some aspects, the subject is administered about 30 mg/day of Compound A, or an equivalent amount of a pharmaceutically acceptable salt thereof, during the second period of treatment. In some aspects, the subject is administered about 40 mg/day of Compound A, or an equivalent amount of a pharmaceutically acceptable salt thereof, during the second period of treatment. In some aspects, the subject is administered about 50 mg/day of Compound A, or an equivalent amount of a pharmaceutically acceptable salt thereof, during the second period of treatment. In some aspects, the subject is administered about 60 mg/day of Compound A, or an equivalent amount of a pharmaceutically acceptable salt thereof, during the second period of treatment. In some aspects, the subject is administered about 70 mg/day of Compound A, or an equivalent amount of a pharmaceutically acceptable salt thereof, during the second period of treatment. In some aspects, the subject is administered about 80 mg/day of Compound A, or an equivalent amount of a pharmaceutically acceptable salt thereof, during the second period of treatment. In some aspects, the subject is administered about 90 mg/day of Compound A, or an equivalent amount of a pharmaceutically acceptable salt thereof, during the second period of treatment. In some aspects, the subject is administered about 100 mg/day of Compound A, or an equivalent amount of a pharmaceutically acceptable salt thereof, during the second period of treatment. In some aspects, the subject is administered about 110 mg/day of Compound A, or an equivalent amount of a pharmaceutically acceptable salt thereof, during the second period of treatment.
- [0176] In some aspects, the initial period of treatment is completed within 7 days. In some aspects, the initial period of treatment is completed within 4 days. In some aspects, the initial period of treatment is completed within 3 days. In some aspects, the initial

period of treatment is completed within 2 days. In some aspects, the initial period of treatment is completed within 1 day.

[0177] In some aspects, the second period of treatment is completed within 7 days. In some aspects, the second period of treatment is completed within 4 days. In some aspects, the second period of treatment is completed within 3 days. In some aspects, the second period of treatment is completed within 2 days. In some aspects, the second period of treatment is completed within 1 day.

[0178] In some aspects, the subject is administered about 30 mg/day of Compound A, or an equivalent amount of a pharmaceutically acceptable salt thereof, during the third period of treatment. In some aspects, the subject is administered about 40 mg/day of Compound A, or an equivalent amount of a pharmaceutically acceptable salt thereof, during the third period of treatment. In some aspects, the subject is administered about 50 mg/day of Compound A, or an equivalent amount of a pharmaceutically acceptable salt thereof, during the third period of treatment. In some aspects, the subject is administered about 60 mg/day of Compound A, or an equivalent amount of a pharmaceutically acceptable salt thereof, during the third period of treatment. In some aspects, the subject is administered about 70 mg/day of Compound A, or an equivalent amount of a pharmaceutically acceptable salt thereof, during the third period of treatment. In some aspects, the subject is administered about 80 mg/day of Compound A, or an equivalent amount of a pharmaceutically acceptable salt thereof, during the third period of treatment. In some aspects, the subject is administered about 90 mg/day of Compound A, or an equivalent amount of a pharmaceutically acceptable salt thereof, during the third period of treatment. In some aspects, the subject is administered about 100 mg/day of Compound A, or an equivalent amount of a pharmaceutically acceptable salt thereof, during the third period of treatment. In some aspects, the subject is administered about 110 mg/day of Compound A, or an equivalent amount of a pharmaceutically acceptable salt thereof, during the third period of treatment.

[0179] In some aspects, the subject is administered about 10 mg/day of Compound A, or an equivalent amount of a pharmaceutically acceptable salt thereof, during the initial period and about 60 mg/day of Compound A, or an equivalent amount of a pharmaceutically acceptable salt thereof, during the second period. In some aspects, the subject is administered about 20 mg/day of Compound A, or an equivalent amount of a

pharmaceutically acceptable salt thereof, during the initial period and about 60 mg/day of Compound A, or an equivalent amount of a pharmaceutically acceptable salt thereof, during the second period. In some aspects, the subject is administered about 30 mg/day of Compound A, or an equivalent amount of a pharmaceutically acceptable salt thereof, during the initial period and about 60 mg/day of Compound A, or an equivalent amount of a pharmaceutically acceptable salt thereof, during the second period. In some aspects, the subject is administered about 40 mg/day of Compound A, or an equivalent amount of a pharmaceutically acceptable salt thereof, during the initial period and about 60 mg/day of Compound A, or an equivalent amount of a pharmaceutically acceptable salt thereof, during the second period.

[0180] In some aspects, the initial period of treatment is completed within 7 days. In some aspects, the initial period of treatment is completed within 4 days. In some aspects, the initial period of treatment is completed within 3 days. In some aspects, the initial period of treatment is completed within 2 days. In some aspects, the initial period of treatment is completed within 1 day. In some aspects, the second period of treatment is completed within 7 days. In some aspects, the second period of treatment is completed within 4 days. In some aspects, the second period of treatment is completed within 3 days. In some aspects, the second period of treatment is completed within 2 days. In some aspects, the second period of treatment is completed within 1 day.

[0181] In some aspects, the subject is administered about 10 mg/day of Compound A, or an equivalent amount of a pharmaceutically acceptable salt thereof, during the first period, about 30 mg/day of Compound A, or an equivalent amount of a pharmaceutically acceptable salt thereof, during the second period, and about 60 mg/day of Compound A, or an equivalent amount of a pharmaceutically acceptable salt thereof, during the third period. In some aspects, the subject is administered about 20 mg/day of Compound A, or an equivalent amount of a pharmaceutically acceptable salt thereof, during the first period, about 40 mg/day of Compound A, or an equivalent amount of a pharmaceutically acceptable salt thereof, during the second period, and about 60 mg/day of Compound A, or an equivalent amount of a pharmaceutically acceptable salt thereof, during the third period. In some aspects, the subject is administered about 30 mg/day of Compound A, or an equivalent amount of a pharmaceutically acceptable salt thereof, during the first period, about 50 mg/day of Compound A, or an equivalent amount of a pharmaceutically

acceptable salt thereof, during the second period, and about 70 mg/day of Compound A, or an equivalent amount of a pharmaceutically acceptable salt thereof, during the third period. In some aspects, the subject is administered about 40 mg/day of Compound A, or an equivalent amount of a pharmaceutically acceptable salt thereof, during the first period, about 60 mg/day of Compound A, or an equivalent amount of a pharmaceutically acceptable salt thereof, during the second period, and about 80 mg/day of Compound A, or an equivalent amount of a pharmaceutically acceptable salt thereof, during the third period.

[0182] In some aspects, the dose titration period of treatment is completed within 5 days. In some aspects, the initial period of treatment is completed within 7 days. In some aspects, the initial period of treatment is completed within 4 days. In some aspects, the initial period of treatment is completed within 3 days. In some aspects, the initial period of treatment is completed within 2 days. In some aspects, the initial period of treatment is completed within 1 day. In some aspects, the second period of treatment is completed within 7 days. In some aspects, the second period of treatment is completed within 4 days. In some aspects, the second period of treatment is completed within 3 days. In some aspects, the second period of treatment is completed within 2 days. In some aspects, the second period of treatment is completed within 1 day.

[0183] In some aspects, the subject is administered a dosage of about 20 mg/day of Compound A, or an equivalent amount of a pharmaceutically acceptable salt thereof, during an initial period of treatment of a dose titration period of treatment, and is administered about 30 mg/day of Compound A, or an equivalent amount of a pharmaceutically acceptable salt thereof, during a second period of treatment of a dose titration period of treatment, then is administered the standard daily dosage of Compound A or an equivalent amount of a pharmaceutically acceptable salt thereof. In some aspects, the standard daily dosage of Compound A is 120 mg/day. In some aspects, the dose titration period of treatment is completed within 21 days. In some aspects, the dose titration period of treatment is completed within 14 days. In some aspects, the dose titration period of treatment is completed within 10 days. In some aspects, the dose titration period of treatment is completed within 7 days. In some aspects, the dose titration period of treatment is completed within 5 days. In some aspects, the initial period of treatment is completed within 7 days. In some aspects, the initial period of

treatment is completed within 4 days. In some aspects, the initial period of treatment is completed within 3 days. In some aspects, the initial period of treatment is completed within 2 days. In some aspects, the initial period of treatment is completed within 1 day. In some aspects, the second period of treatment is completed within 7 days. In some aspects, the second period of treatment is completed within 4 days. In some aspects, the second period of treatment is completed within 3 days. In some aspects, the second period of treatment is completed within 2 days. In some aspects, the second period of treatment is completed within 1 day.

EXAMPLES

EXAMPLE 1: Preparation of Crystalline Form A of Compound A

- [0184]** Crystal forms can be prepared by a variety of methods, including for example, crystallization or recrystallization from a suitable solvent, sublimation, growth from a melt, solid state transformation from another phase, crystallization from a supercritical fluid, and jet spraying. Techniques for crystallization or recrystallization of co-crystal forms from a solvent mixture include, for example, evaporation of the solvent, decreasing the temperature of the solvent mixture, crystal seeding a supersaturated solvent mixture of the molecule and/or salt, freeze drying the solvent mixture, and addition of antisolvents (countersolvents) to the solvent mixture.
- [0185]** For crystallization techniques that employ solvent, the choice of solvent or solvents is typically dependent upon one or more factors, such as solubility of the compound, crystallization technique, and vapor pressure of the solvent. Combinations of solvents can be employed, for example, the compound can be solubilized into a first solvent to afford a solution, followed by the addition of an antisolvent to decrease the solubility of the compound in the solution and to afford the formation of crystals. An antisolvent is a solvent in which the compound has low solubility.
- [0186]** In one method to prepare crystals, a compound is suspended and/or stirred in a suitable solvent to afford a slurry, which can be heated to promote dissolution. The term “slurry”, as used herein, means a saturated solution of the compound, which can also contain an additional amount of the compound to afford a heterogeneous mixture of the compound and a solvent at a given temperature.

- [0187] Seed crystals can be added to any crystallization mixture to promote crystallization. Seeding can be employed to control growth of a particular polymorph or to control the particle size distribution of the crystalline product. Accordingly, calculation of the amount of seeds needed depends on the size of the seed available and the desired size of an average product particle as described, for example, in "Programmed Cooling of Batch Crystallizers," J.W. Mullin and J. Nyvlt, *Chemical Engineering Science*, 1971,26, 369-377. In general, seeds of small size are needed to control effectively the growth of crystals in the batch. Seed of small size can be generated by sieving, milling, or micronizing of large crystals, or by micro-crystallization of solutions. Care should be taken that milling or micronizing of crystals does not result in any change in crystallinity from the desired crystal form (i.e., change to amorphous or to another polymorph).
- [0188] A cooled crystallization mixture can be filtered under vacuum, and the isolated solids can be washed with a suitable solvent, such as cold recrystallization solvent, and dried under a nitrogen purge to afford the desired crystalline form. The isolated solids can be analyzed by a suitable spectroscopic or analytical technique, such as solid state nuclear magnetic resonance, differential scanning calorimetry, x-ray powder diffraction, or the like, to assure formation of the preferred crystalline form of the product. The resulting crystalline form is typically produced in an amount of greater than about 70 weight % isolated yield, preferably greater than 90 weight % isolated yield, based on the weight of the compound originally employed in the crystallization procedure. The product can be comilled or passed through a mesh screen to delump the product, if necessary.
- [0189] The presence of more than one polymorph in a sample can be determined by techniques such as powder x-ray diffraction (PXRD) or by Raman or IR spectroscopy solid state nuclear magnetic resonance spectroscopy. For example, the presence of extra peaks in the comparison of an experimentally measured PXRD pattern with a simulated PXRD pattern can indicate more than one polymorph in the sample. The simulated PXRD can be calculated from single crystal x-ray data. see Smith, D.K., "*A FORTRAN Program for Calculating X-Ray Powder Diffraction Patterns*," Lawrence Radiation Laboratory, Livermore, California, UCRL-7196 (April 1963).

[0190] The crystalline form of Compound A according to the invention can be characterized using various techniques, the operation of which are well known to those of ordinary skill in the art. The forms can be characterized and distinguished using single crystal x-ray diffraction, which is based on unit cell measurements of a single crystal of form at a fixed analytical temperature. A detailed description of unit cells is provided in Stout & Jensen, X-Ray Structure Determination: A Practical Guide, Macmillan Co., New York (1968), Chapter 3, which is herein incorporated by reference. Alternatively, the unique arrangement of atoms in spatial relation within the crystalline lattice can be characterized according to the observed fractional atomic coordinates. Another means of characterizing the crystalline structure is by powder x-ray diffraction analysis in which the diffraction profile is compared to a simulated profile representing pure powder material, both run at the same analytical temperature, and measurements for the subject form characterized as a series of 2θ values (usually four or more).

[0191] Other means of characterizing the form can be used, such as solid state nuclear magnetic resonance (SSNMR), differential scanning calorimetry, thermogravimetric analysis and FT-Raman and FT-IR. These techniques can also be used in combination to characterize the subject form. In addition to the techniques specifically described herein, the presence of a particular crystalline form can be determined by other suitable analytical methods.

Example 1A

[0192] 150 mg Compound A was dissolved in 1.5 mL tetrahydrofuran (THF) at 20 °C. 0.5 mL of this solution was subjected to flash evaporation using a centrifugal evaporator to yield solids of Form A. 0.5 mL of the same solution was subjected to slow evaporation at 20 °C to yield solids of Form A.

Example 1B

[0193] 200 mg Compound A was dissolved in 1 mL dichloromethane (DCM) at 20 °C. 0.5 mL of this solution was subjected to flash evaporation using a centrifugal evaporator to yield solids of Form A. 0.5 mL of the same solution was subjected to slow evaporation at 20 °C to yield solids of Form A.

Example 1C

- [0194] 100 mg of Compound A was dissolved in 0.5 mL of THF at 50 °C and kept stirring at 20 °C. 0.5 mL of water was added to the clear solution, which resulted in solids of Form A.

Example 1D

- [0195] 100 mg of Compound A was dissolved in 1 mL of 2-methyl THF at 50 °C and kept stirring at 20 °C. 1 mL of n-heptane was added to the clear solution, which resulted in solids of Form A.

Example 1E

- [0196] A solution of Compound A in *tert*-Amyl alcohol (t-AmOH) was concentrated to 4 L/kg under vacuum, then was charged with 15 L/kg DCM and 10 L/kg water. Layers were split and the DCM layer was concentrated to 4 L/kg under vacuum. The DCM layer was charged with 8-10 L/kg ethyl acetate (EtOAc) and then concentrated to 4 L/kg under vacuum. An additional 8-10 L/kg EtOAc was charged then concentrated to 4 L/kg under vacuum. 6-8 L/kg EtOAc was charged and warmed to 70-83°C until complete dissolution. The resulting slurry was cooled to 0-10°C over at least 2 hours, followed by aging for at least an additional 12 hours. The slurry was filtered. The wet cake was washed with 3-5 L/kg EtOAc and dried under vacuum at 55-60°C to yield solids of Form A.

Example 1F

- [0197] A solution of Compound A in t-AmOH was concentrated to 4 L/kg at 55 °C under vacuum, was then charged with 5 L/kg 2-propanol (IPA) and concentrated to 4 L/kg at 55 °C under vacuum. This process was repeated two additional times with 2 x 5 L/kg IPA. The batch was cooled to 30°C, was then charged with 1.3 L/kg water and heated to 45-55 °C. The resulting warm solution was polish filtered and cooled to 30 °C. 1 wt% Form A seeds were charged, followed by 2 L/kg water. After at least 6 hours, an additional 8.7 L/kg water was charged. The resulting slurry was cooled to 20 °C over at least 30 minutes, and the slurry was aged at least 3 hours. The solids were filtered and the wet cake was sequentially washed with 3 L/kg water:IPA:t-AmOH mixture (11:3:1 by volume) and 3 L/kg water, and dried under vacuum at 50-60 °C to solids of Form A.

Example 1G

[0198] To a solution of isopropyl (1S,3S)-3-((2-methyl-6-(1-methyl-5-(((methyl(propyl)carbamoyl)oxy) methyl)-1H-1,2,3-triazol-4-yl)pyridin-3-yl)oxy)cyclohexane-1-carboxylate (500 mg, 1.025 mmol) in 1:1 THF/MeOH (10 mL) was added aqueous LiOH (1.538 mL of a 2M solution, 3.08 mmol). The reaction mixture was stirred at 50 °C for 1h, then was cooled to RT, and organic volatiles were removed in vacuo. The concentrated solution was washed with EtOAc, then was acidified to pH ~6-7 (1N aq HCl). This aqueous layer was extracted with EtOAc several times. The combined organic extracts were washed with water, dried (MgSO₄) and the MgSO₄ was filtered off. The EtOAc solution was concentrated in vacuo to yield solids of Form A.

[0199] The analytical data for the crystalline Compound A described herein were obtained using the following procedures.

Single Crystal

[0200] Single crystal X-ray data were collected using a Bruker X8 Kappa diffractometer equipped with an APEX II CCD detector and a MICROSTAR microfocus rotating anode X-ray generator of monochromatic Cu K α radiation. The single crystal was at room temperature during data collection.

[0201] Indexing and processing of the measured intensity data were carried out with the APEX2 program suite (Bruker AXS, Inc., 5465 East Cheryl Parkway, Madison, WI 53711 USA). The final unit cell parameters were determined using the full data set. The structures were solved by direct methods and refined by full-matrix least-squares approach using the SHELXTL software package (G. M. Sheldrick, SHELXTL v6.14, Bruker AXS, Madison, WI USA.). Structure refinements involved minimization of the function defined by $\sum w(|F_o| - |F_c|)^2$, where w is an appropriate weighting factor based on errors in the observed intensities, F_o is the structure factor based on measured reflections, and F_c is the structure factor based on calculated reflections. Agreement between the refined crystal structure model and the experimental X-ray diffraction data is assessed by using the residual factors $R = \sum ||F_o| - |F_c|| / \sum |F_o|$ and $wR = [\sum w(|F_o| - |F_c|)^2 / \sum w|F_o|]^2$. Difference Fourier maps were examined at all stages of refinement. All non-hydrogen atoms were refined with anisotropic thermal displacement parameters. Hydrogen atoms

were introduced using idealized geometry with isotropic temperature factors and included in structure factor calculations with fixed parameters.

Powder X-Ray Diffraction (PXRD)

- [0202] PXRD diffractogram was acquired on a Bruker D8 Advance system using Cu K α (40 kV/40 mA) radiation and a step size of 0.03° 2 θ and LynxEye detector, over a 2 θ range of 2-40°. Configuration on the incident beam side: Göebel mirror, mirror exit slit (0.2 mm), 2.5 deg Soller slits, beam knife. Configuration on the diffracted beam side: anti-scatter slit (8 mm) and 2.5 deg. Soller slits. Sample was mounted flat on zero-background Si wafers.

Differential Scanning Calorimetry (DSC)

- [0203] DSC was conducted with a TA Instruments Q2000 differential scanning calorimeter equipped with an autosampler and a refrigerated cooling system under 40 mL/min N₂ purge for the Q2000. DSC thermogram was obtained at 15 °C/min in crimped Al pan.

Thermal Gravimetric Analysis (TGA)

- [0204] TGA thermograms were obtained with a TA Instruments Q500 thermogravimetric analyzer under 40 mL/min N₂ purge for balance and 60 mL/min for sample in Al pan. TGA thermogram was obtained at 15 °C/min.

Moisture Sorption Isotherms

- [0205] Moisture sorption isotherms were collected in a TA Instrument VTI-SA+ Vapor Sorption Analyzer using approximately 270 mg of sample in a 250 μ L ceramic pan. The sample was dried at 30 °C until the loss rate of 0.005 wt %/min was obtained for 10 minutes. The sample was tested at 25 °C and 4, 5, 15, 25, 35, 45, 50, 65, 75, 85, and 95% RH. Equilibration at each RH was reached when the rate of 0.01 wt%/min for 35 minutes was achieved or a maximum of 600 minutes.

EXAMPLE 2. A Double-Blind, Placebo-Controlled, Randomized, Single and Multiple Ascending Dose Study of the Safety, Pharmacokinetics, and Exploratory Pharmacodynamics of Oral Administration of Compound A in Healthy Participants

- [0206] The study was performed in 3 parts in 112 healthy male and female participants, including 24 Japanese participants. Female participants were to be not of childbearing potential. The present study was designed to evaluate the safety and tolerability, PK, and exploratory PD of an oral suspension of Compound A. Parts A and B (Cohort B1 only) enrolled healthy participants and was conducted at a site in The Netherlands and Part B (Cohort B2 to B5) enrolled healthy non-Japanese participants and was conducted at a site in the United Kingdom (UK). Part C enrolled healthy Japanese participants and was conducted at the same site in the UK.
- [0207] Part A was an SAD study in a planned number of 6 sequential dose escalation cohorts (3, 10, 30, 100, 150, or 250 mg) of 8 healthy participants (6 active + 2 placebo) each, under fasted conditions. Eligible participants in Part A (excluding those in Cohort A7 [food effect (FE)/pH cohort]) received a single administration of study drug (Compound A or placebo) under fasted conditions. In Cohort A1 to Cohort A6, sentinel dosing was employed (1 active + 1 placebo, followed after 48 hours by the remaining participants of the cohort [5 active + 1 placebo]). However, in Cohort A6 (250 mg) only the 2 sentinel participants were dosed before discontinuing further enrollment, due to dose-limiting events observed in a sentinel participant. In addition to the 6 ascending dose cohorts, a cohort of 6 healthy participants (Cohort A7; 6 active, 100 mg Compound A) was included to assess the effect of food and pH on the bioavailability of Compound A in a 3-period, open-label, fixed-sequence, crossover design (FE/pH cohort).
- [0208] Part B was a MAD study in a planned number of 6 sequential dose escalation cohorts (10 mg QD, 30 mg QD, 30 mg BID, 60 mg BID, 125 mg BID, and ≤ 250 mg BID) of 8 healthy participants (6 active + 2 placebo) each, under fasted conditions. However, Cohort B6 (≤ 250 mg BID) was cancelled because sufficient safety and PK data had been obtained at doses up to 125 mg BID. Eligible participants received study drug (Compound A or placebo) administered orally for 14 days.
- [0209] Part C was a MAD study in 3 sequential dose escalation cohorts (30 mg BID, 60 mg BID, and 90 mg BID) of 8 healthy Japanese participants (6 active + 2 placebo) each. Eligible participants in Cohorts C1 to C3 received study drug (Compound A or placebo) administered orally for 14 days.
- [0210] Physical examinations, vital sign measurements (including orthostasis testing in Cohort A6, Cohort B3 to B5, and C1 to C3 at selected time points), 12-lead

electrocardiogram (ECG), and clinical laboratory evaluations were performed at selected times throughout the study. In addition, Holter monitoring was performed for the first 24 hours post dose on Day 1 in Part A (not in FE/pH cohort), and also for the first 24 hours post dose on Day 1 and Day 14 in Parts B and C. Participants were closely monitored for adverse events (AEs). Blood samples were collected for up to 14 days (follow-up visit) after (last) study drug administration for PK analysis. In addition, blood and urine were collected for exploratory biomarker assessments and for biobanking of samples for potential analyses. Urine was collected for potential PK analysis for up to 96 hours after a single dose of Compound A or placebo was administered in the SAD part, and for up to 24 hours after the first (morning) dose of study drug on Day 1 and for up to 24 hours after the last (morning) dose of study drug on Day 14 in the MAD parts.

[0211] Compound A was generally safe and well tolerated following single and multiple dose oral administration to healthy participants. It was observed that Compound A was associated with reversible reductions in BP that generally reached a maximum 4 to 8 hours after dosing and were not associated with meaningful changes in heart rate. BP reductions were mostly asymptomatic.

[0212] In the SAD cohorts, Compound A decreased SBP and DBP dose dependently, reversibly, and mostly asymptotically with minimal effect on heart rate. Changes in blood pressure are shown in Tables 3 and 4 below.

Table 3: Maximum of Mean ($\pm$ SD) Reduction in Systolic and Diastolic Blood Pressure from Baseline and Corresponding Time in SAD within 12 Hours Post Dose

Dose (mg) (Cohort)	SBP (mmHg)			DBP (mmHg)		
	Baseline (mmHg)	Reduction (mmHg)	Time (h)	Baseline (mmHg)	Reduction (mmHg)	Time (h)
Placebo	124.3 $\pm$ 15.43	0.5 $\pm$ 10.16	12	70.5 $\pm$ 6.38	4.5 $\pm$ 7.69	5
3 (A1)	124.7 $\pm$ 13.00	5.2 $\pm$ 3.43	2	71.2 $\pm$ 8.28	6.7 $\pm$ 3.14	6
					6.7 $\pm$ 5.82 ^a	12
10 (A2)	119.0 $\pm$ 10.43	9.5 $\pm$ 16.13	8	71.0 $\pm$ 7.82	8.8 $\pm$ 9.91	6
30 (A3)	117.7 $\pm$ 11.38	11.7 $\pm$ 7.61	4	70.3 $\pm$ 4.46	6.8 $\pm$ 1.72	5
100 (A4)	116.5 $\pm$ 7.09	15.5 $\pm$ 11.59	2	65.7 $\pm$ 7.81	9.7 $\pm$ 8.64	5

100 fasted (A7)	123.8 ± 8.98	25.8 ± 9.54	8	74.8 ± 4.96	12.5 ± 7.06	5
100 fasted +famotidine (A7)	121.7 ± 9.75	19.3 ± 17.41	6	73.3 ± 7.39	11.8 ± 8.40	6
100 fed (A7)	115.5 ± 7.37	18.5 ± 12.94	6	68.2 ± 3.54	12.7 ± 4.18	5
150 (A5)	116.3 ± 11.34	16.5 ± 8.41	6	63.7 ± 11.62	12.7 ± 5.61	6

DBP = diastolic blood pressure; SAD = single ascending dose; SBP=systolic blood pressure; SD = standard deviation

^a Identical maximum reduction to an earlier measurement

Note: Baseline is defined as the last observation recorded before the first study drug administration in each period. Time (h) is the time since the last morning study drug administration.

Table 4: Mean (± SD) Systolic and Diastolic Blood Pressure in SAD within 24 Hours Post Dose

	Placebo	3 mg	10 mg	30 mg	100 mg	150 mg	100 mg Fasted	100 mg Fasted + Famotidine	100 mg Fed
N	11	6	6	6	6	6	6	6	6
SBP									
Baseline	124.3 (15.43)	124.7 (13.00)	119.0 (10.43)	117.7 (11.38)	116.5 (7.09)	116.3 (11.34)	123.8 (8.98)	121.7 (9.75)	115.5 (7.37)
D1 2h	125.1 (10.19)	119.5 (13.00)	112.2 (7.19)	107.5 (11.57)	101.0 (11.14)	105.0 (14.04)	107.5 (12.06)	111.3 (13.63)	100.5 (16.81)
D1 4h	124.9 (10.87)	120.3 (10.33)	110.2 (6.24)	106.0 (10.16)	101.3 (13.29)	101.5 (7.74)	103.8 (10.30)	106.5 (14.46)	104.2 (11.27)
D1 8h	124.8 (11.11)	124.5 (10.37)	109.5 (9.22)	113.8 (17.70)	105.0 (7.13)	107.2 (12.86)	98.0 (10.77)	105.0 (13.19)	100.3 (17.13)
D2 24h	121.3 (18.24)	118.8 (6.59)	118.5 (12.96)	120.2 (12.69)	114.2 (6.11)	114.7 (12.18)	115.2 (6.85)	118.7 (9.48)	112.8 (5.67)
DBP									
Baseline	70.5 (6.38)	71.2 (8.28)	71.0 (7.82)	70.3 (4.46)	65.7 (7.81)	63.7 (11.62)	74.8 (4.96)	73.3 (7.39)	68.2 (3.54)
D1 2h	72.2 (7.88)	68.3 (9.83)	67.7 (3.27)	66.2 (3.19)	59.0 (5.97)	58.2 (7.36)	67.2 (5.00)	67.2 (4.75)	57.2 (5.49)
D1 4h	70.3 (7.39)	69.5 (10.67)	68.7 (4.41)	65.2 (4.71)	58.7 (7.61)	56.0 (4.69)	64.2 (2.86)	65.3 (4.93)	58.2 (7.68)
D1 8h	69.6 (8.44)	68.0 (4.90)	63.0 (4.73)	65.2 (4.83)	56.3 (7.58)	57.8 (5.60)	63.0 (6.66)	63.2 (4.49)	58.8 (5.31)
D2 24h	70.1 (5.86)	68.7 (5.32)	71.7 (7.42)	71.0 (4.73)	66.0 (10.71)	66.2 (10.72)	69.3 (2.34)	71.7 (4.63)	69.3 (3.72)

DBP = diastolic blood pressure, SAD = single ascending dose; SBP = systolic blood pressure; SD = standard deviation

Note: Baseline is defined as the last observation recorded before the first study drug administration in each period. Time (h) is the time since the last morning study drug administration.

[0213] In the MAD cohorts, reversible reductions in mean SBP and DBP occurred in all groups except for the placebo QD group, which showed no change in BP. In the QD groups, reductions generally occurred in a Compound A dose-dependent manner. In the BID groups, both placebo and Compound A treatment resulted in reductions in BP, and there were no clear differences between placebo and the Compound A groups. There were no clear changes in the magnitude of BP reductions with repeated dosing over the 14-day treatment period. In the Japanese MAD cohorts, reversible reductions in mean BP occurred in all groups, including placebo. There was no clear Compound A dose-dependent BP reduction trend. Changes in blood pressure can be found in Tables 5-7 shown below.

Table 5: Maximum of Mean ($\pm$ SD) Reduction in Systolic and Diastolic Blood Pressure from Baseline and Corresponding Time – Part B (MAD Cohorts)

Dose (mg)	SBP			DBP (mmHg)		
	Baseline (mmHg)	Reduction (mmHg)	Time (Day-h)	Baseline (mmHg)	Reduction (mmHg)	Time (Day-h)
Placebo QD	113.8 $\pm$ 8.14	6.0 $\pm$ 6.78	9-0	66.3 $\pm$ 5.50	0.5 $\pm$ 5.69	12-0
					0.5 $\pm$ 7.23	14-2
10 QD (B1)	115.2 $\pm$ 14.03	6.7 $\pm$ 11.83	2-0	69.0 $\pm$ 11.37	6.8 $\pm$ 2.64	1-5
		6.7 $\pm$ 11.36	13-0			
30 QD (B2)	112.2 $\pm$ 13.96	10.7 $\pm$ 7.06	14-8	70.7 $\pm$ 7.76	8.8 $\pm$ 4.62	14-5
Placebo BID	124.8 $\pm$ 8.75	20.2 $\pm$ 10.11	13-0	64.5 $\pm$ 6.16	8.7 $\pm$ 10.63	14-5
30 BID (B3)	121.3 $\pm$ 11.43	15.8 $\pm$ 10.19	1-5	70.0 $\pm$ 3.46	11.2 $\pm$ 4.58	1-5
60 BID (B4)	123.2 $\pm$ 8.68	17.5 $\pm$ 11.31	17-0	68.2 $\pm$ 3.82	8.3 $\pm$ 6.89	3-4
125 BID (B5)	118.5 $\pm$ 7.84	14.5 $\pm$ 5.86	9-0	69.7 $\pm$ 3.83	14.7 $\pm$ 5.68	12-12

BID = twice daily; DBP = diastolic blood pressure; MAD = multiple ascending dose; QD = once daily; SBP = systolic blood pressure; SD = standard deviation

Note: Baseline is defined as the last observation recorded before the first study drug administration in each period. Time (h) is the time since the last morning study drug administration

Table 6: Mean ($\pm$ SD) Systolic and Diastolic Blood Pressure in MAD
within 24 Hours Post First and Last Dose

	Placebo QD	10 mg QD	30 mg QD	Placebo BID	30 mg BID	60 mg BID	125 mg BID
N	4	6	6	6	6	6	6
SBP							
Baseline	113.8 (8.14)	115.2 (14.03)	112.2 (13.96)	124.8 (8.75)	121.3 (11.43)	123.2 (8.68)	118.5 (7.84)
D1 2h	118.8 (10.40)	112.2 (18.74)	104.8 (10.23)	120.3 (5.79)	106.5 (6.72)	110.2 (5.81)	112.2 (12.45)
D1 4h	115.5 (12.56)	109.5 (18.06)	102.3 (6.59)	118.7 (7.92)	107.2 (6.59)	106.7 (7.55)	112.2 (11.57)
D1 8h	117.3 (11.00)	112.8 (20.93)	107.2 (9.56)	111.3 (8.82)	106.3 (5.92)	109.3 (10.15)	107.3 (14.43)
D2 24h	114.3 (5.91)	108.5 (17.35)	114.3 (8.41)	114.2 (10.68)	114.7 (6.15)	118.8 (9.35)	118.8 (18.74)
D14 312h	113.0 (11.92)	112.8 (15.89)	110.0 (14.82)	108.5 (4.89)	119.7 (8.21)	111.8 (7.52)	111.3 (8.48)
D14 314h	111.3 (8.10)	113.5 (16.13)	101.7 (5.75)	110.2 (4.62)	109.7 (12.26)	110.5 (5.92)	116.0 (8.51)
D14 317h	119.0 (15.64)	114.5 (18.80)	102.3 (10.48)	113.2 (7.19)	114.3 (5.96)	114.8 (11.57)	116.3 (9.35)
D14 320h	112.5 (12.37)	111.2 (17.61)	101.5 (9.95)	109.5 (8.24)	110.0 (7.21)	115.5 (7.56)	114.5 (13.62)
D15 336h	113.3 (13.23)	110.8 (18.05)	107.3 (9.67)	110.5 (4.76)	116.3 (5.32)	114.5 (6.72)	111.3 (10.75)
DBP							
Baseline	66.3 (5.50)	69.0 (11.37)	70.7 (7.76)	64.5 (6.16)	70.0 (3.46)	68.2 (3.82)	69.7 (3.83)
D1 2h	70.5 (5.20)	70.2 (15.96)	66.5 (4.97)	67.7 (5.92)	63.3 (4.37)	64.5 (3.33)	62.3 (7.12)
D1 4h	69.5 (4.43)	65.8 (13.32)	67.8 (6.59)	67.2 (4.02)	62.7 (3.98)	66.0 (6.23)	64.7 (1.97)
D1 8h	70.0 (7.02)	68.7 (12.31)	66.0 (7.92)	60.5 (10.15)	63.2 (1.94)	64.7 (2.94)	64.7 (4.46)
D2 24h	67.8 (4.19)	65.3 (11.06)	67.3 (9.14)	62.7 (7.76)	66.7 (5.82)	65.7 (4.97)	66.3 (2.94)
D14 312h	70.0 (5.48)	69.3 (10.23)	63.3 (4.76)	58.7 (8.91)	68.7 (4.80)	64.8 (6.71)	62.0 (7.90)
D14 314h	65.8 (6.85)	67.5 (12.69)	63.5 (3.08)	62.0 (6.99)	63.8 (3.43)	64.0 (6.84)	65.0 (3.29)

D14 317h	66.5 (7.68)	64.3 (8.09)	61.8 (5.38)	55.8 (7.65)	61.0 (5.37)	62.5 (5.17)	59.2 (7.63)
D14 320h	70.0 (8.04)	67.5 (10.45)	63.2 (5.12)	57.7 (8.78)	617 (3.78)	63.0 (4.15)	61.8 (6.11)
D15 336h	66.5 (8.89)	66.8 (9.83)	62.3 (5.28)	60.7 (5.99)	65.3 (3.88)	64.5 (3.67)	63.0 (6.00)

BID = twice daily; DBP = diastolic blood pressure; MAD = multiple dose; QD = once daily; SBP=systolic blood pressure; SD = standard deviation

Note: Baseline is defined as the last observation recorded before the first study drug administration in each period. Time (h) is the time since the last morning study drug administration.

Table 7: Maximum of Mean ($\pm$ SD) Reduction in Systolic and Diastolic Blood Pressure from Baseline and Corresponding Time - Part C (MAD Japanese Cohorts)

Dose (mg)	SBP			DBP (mmHg)		
	Baseline (mmHg)	Reduction (mmHg)	Time (Day-h)	Reduction (mmHg)	Baseline (mmHg)	Time (Day-h)
Placebo BID	118.7 $\pm$ 8.57	12.5 $\pm$ 9.20	2-16	76.5 $\pm$ 7.94	11.2 $\pm$ 7.36	2-16
30 BID (C1)	117.5 $\pm$ 5.82	15.0 $\pm$ 6.84	1-4	72.2 $\pm$ 3.87	8.8 $\pm$ 5.12	14-6
60 BID (C2)	114.8 $\pm$ 10.26	13.0 $\pm$ 8.22	2-16	73.8 $\pm$ 6.18	8.2 $\pm$ 10.40	4-16
90 BID (C2)	111.5 $\pm$ 8.12	11.8 $\pm$ 8.47	1-6	70.7 $\pm$ 7.58	8.0 $\pm$ 8.22	1-6

BID = twice daily; DBP = diastolic blood pressure; MAD = multiple ascending dose; SBP = systolic blood pressure. Note: Baseline is defined as the last observation recorded before the first study drug administration in each period. Time (h) is the time since the last morning study drug administration.

EXAMPLE 3. A Double-Blind, Placebo-Controlled, Randomized, Single and Multiple Ascending Dose Study of the Safety, Tolerability and Pharmacokinetics of Oral Administration of Compound A in Healthy Chinese participants.

[0214] Single dose of 60 mg and multiple doses of 60 mg BID are selected for this China PK bridging study to allow PK, safety and tolerability for clinically relevant doses. It will investigate the effect of genetic variations in genes associated with drug absorption, distribution, metabolism, excretion, and transport on the PK of Compound A in healthy Chinese participants.

Single dose

- [0215] On Day 1, eligible subjects will be randomized in a 3:1 ratio to a single oral dose of Compound A or matching placebo. Participants will fast for at least 10 hours prior to dosing, and participants will remain fasted until at least 4 hours after administration.

Multiple dose

- [0216] On Day 5 through Day 10, subjects will receive Compound A BID or matching placebo. On Day 11, subjects will receive a morning dose (last dose) of Compound A or matching placebo.
- [0217] On Days 5 and 11, participants will fast for at least 10 hours prior to dosing, and participants will remain fasted until at least 4 hours after administration of the morning dose.
- [0218] In the mornings of Days 6-10, participants will also be dosed in the fasted state; however, approximately 2 hours after dosing on these days, they will receive breakfast.
- [0219] In the evenings of Days 5-10, participants will receive a second oral dose of Compound A or placebo, 12 hours after the morning dose. The evening dose will be administered approximately 2 hours after start of dinner.
- [0220] Study treatment will be administered with 240 mL of water.

EXAMPLE 4: A Multicenter, Randomized, Double-blind, Placebo-controlled, Phase 2 Study of the Efficacy, and the Safety and Tolerability of Compound A in Participants with Pulmonary Fibrosis

- [0221] Safety and efficacy topline data from the final analysis of the IPF cohort in the Phase 2 Study support the continued development of Compound A in both IPF and PPF. A schematic showing the outline of both cohorts of the trial is shown in FIG. 7.

EXAMPLE 4A: IPF Cohort

- [0222] A total of 278 participants with IPF were randomized and 276 participants were treated as of the final analyses data cut-off (04-Aug-2022). Male and female participants ≥ 40 years of age with IPF and percent predicted forced vital capacity (ppFVC) $\geq 40\%$ and percent predicted DLCO (ppDLCO) $\geq 25\%$; diagnosed within 7 years of screening; having a centrally-read chest HRCT obtained at screening that was consistent with UIP or

probable UIP, or having a lung biopsy consistent with UIP were eligible to enter the study. The mean baseline ppFVC for all subjects was 76.5%. In the primary IPF cohort, participants were randomized (1:1:1) to receive 30 mg or 60 mg Compound A or placebo (PBO) twice daily for 26 weeks. Participants were stratified by standard of care (SoC) IPF therapy (pirfenidone versus nintedanib versus none) and region (Japan versus Rest of World) at randomization.

[0223] The primary objective of the study was to determine the rate of change in ppFVC from baseline to Week 26. The primary objective was evaluated with a two estimand framework to handle the intercurrent event of dose reduction to 10 mg BID or matching PBO when pre-specified low BP criteria is met. The primary estimand is adopted to estimate treatment effect when dose reduction is implemented. The supplementary estimand is adopted to estimate the effect of treatment without dose reduction.

[0224] Of the 276 treated participants that contributed to these analyses, 90% (n=248) completed the 26-week treatment phase and 10% (n=28) were treatment discontinued. Treatment discontinuations due to TEAEs were evenly balanced across treatment groups (PBO: 9.8%; 30mg: 9.9%; 60 mg: 6.5%).

[0225] Table 8 shows the baseline demographics and clinical characteristics of the subject population in the IPF cohort.

Table 8: Baseline Demographics and Clinical Characteristics

Parameter*	IPF Cohort		
	Placebo (n=92)	30-mg Compound A (n=91)	60-mg Compound A (n=93)
<i>Demographics</i>			
Age, years	69.0±6.7	69.5±7.3	68.8±7.9
Male sex, no. (%)	76 (82.6)	77 (84.6)	69 (74.2)
Race, no. (%)			
White	65 (70.7)	64 (70.3)	64 (68.8)
Asian	25 (27.2)	25 (27.5)	27 (29.0)
Other	2 (2.2)	2 (2.2)	2 (2.2)
<i>Clinical characteristics</i>			
Weight, kg	76.5±15.0	76.5±14.1	75.8±15.6
BMI, kg/m ²	27.2±4.1	26.9±4.0	27.1±4.5
Cigarette smoking history, no. (%)			
Never	32 (34.8)	30 (33.0)	31 (33.3)
Current	1 (1.1)	1 (1.1)	2 (2.2)

Former	59 (64.1)	60 (65.9)	60 (64.5)
Concurrent background treatment [†] , no. (%)			
Pirfenidone	26 (28.3)	26 (28.6)	25 (26.9)
Nintedanib	36 (39.1)	36 (39.6)	37 (39.8)
None	30 (32.6)	29 (31.9)	31 (33.3)
Time since diagnosis, years	2.7±1.7	2.8±1.6	2.8±1.7
No.	89	82	84
FVC, mL	2741±810	2768±770	2641±768
FVC, percent of predicted	77±19	77±19	76±17
No.	65	66	68
DL _{co} , percent of predicted, hemoglobin-corrected	51.2±18.6	47.8±14.3	48.4±17.3
No.	80	81	82
6MWT, meters	389.4±113.8	399.3±102.1	401.8±115.7
No.	89	88	90
Quantitative lung fibrosis (HRCT), %	17.3±11.0	17.3±10.8	17.2±10.4

*Values before and after plus-minus symbols represent means ± SD. [†]Patients with PPF were permitted to remain on background antifibrotics ± ILD-targeted immunosuppressants (see Supplementary Table S1). 6MWT, 6-minute walk test; BMI, body mass index; DL_{co}, diffusing capacity of the lung for carbon monoxide; FVC, forced vital capacity; HRCT, high-resolution computed tomography; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; PPF, progressive pulmonary fibrosis; SD, standard deviation.

[0226] Summary results are described in Tables 9-12; and additional results from the final analysis from the IPF cohort are described below.

Primary Estimand:

[0227] Analysis Strategy: The primary estimand was to evaluate the efficacy of Compound A at 30 mg or 60 mg twice daily, compared to PBO in IPF participants who met the enrollment criteria, with or without use of SoC. The rate of decline in ppFVC (%) from baseline to Week 26 was compared using the difference between each dose and PBO as a population level summary regardless of dose reduction or treatment discontinuation for any reason (treatment policy strategy).

Efficacy Results based on Primary Estimand:

[0228] In the overall population, the 60 mg dose group showed favorable treatment responses at Week 26, measured as rate of decline of ppFVC and decline of FVC (mL), compared to PBO under both primary estimand and the supplementary estimand

frameworks (Table 9). The 30 mg dose group did not demonstrate efficacy (data not shown).

[0229] In the overall population, the 60 mg dose showed a treatment difference in the rate of decline in ppFVC of 1.45 ± 0.81 (mean $\pm$ standard error of the mean [SEM]) [95% CI - 0.133, 3.028]. This corresponds to an overall relative reduction of 54%, compared to PBO slope of decline (-2.67 ± 0.57).

[0230] When analyzing the rate of decline in FVC in mL (adjusted for age, gender, and height as measured by the slope difference of the 60 mg arm [-54.3 ± 20.76] by the difference in slope of the PBO arm [-101.2 ± 20.45]), the 60 mg dose corresponds to a 46.9 ml relative treatment difference compared to PBO (46.9 ± 29.14 (mean $\pm$ SEM) [95% CI -10.3, 104.1]).

[0231] Subgroup analyses of background SoC (SoC vs none) demonstrated favorable responses on the primary endpoint in the 60 mg group in contrast to the PBO group.

[0232] Of those on background SoC (68% of the overall population), the 60 mg dose showed a treatment difference versus PBO of 1.22 ± 0.87 (mean $\pm$ SEM) [95% CI - 0.486, 2.929], which corresponds to a 39% relative treatment benefit compared to PBO.

[0233] Of those not on background SoC (32% of the overall population), the 60 mg dose showed a treatment difference versus PBO of 2.01 ± 1.7 (mean $\pm$ SEM) [95% CI -1.327, 5.355], which corresponds to a 113% relative treatment benefit compared to PBO.

Supplementary Estimand:

[0234] Analysis Strategy: The supplementary estimand for the primary objective is to evaluate the efficacy of Compound A at 30 mg or 60 mg twice daily without dose reduction, compared to the PBO in IPF subjects who met the enrollment criteria, with or without use of SoC. The rate of decline in ppFVC (%) from baseline to Week 26 has been compared using the difference between each dose and PBO as a population level summary regardless of treatment discontinuation for any reason (treatment policy strategy). In the event of dose reduction, data collected after dose reduction will not be considered relevant to the treatment effect of interest and therefore, will be treated as missing (while-on-treatment strategy).

[0235] Dose reductions to Compound A 10 mg BID vs. matching PBO were implemented due to protocol-defined low BP criteria in 18 (6.5%) participants and

approximately evenly distributed across arms (PBO: 5 (5.4%); 30 mg: 7 (7.7%); 60 mg: 6 (6.5%))

- [0236] In the overall population, the 60 mg dose showed a treatment difference in the rate of decline in ppFVC of 1.77 ± 0.82 (mean $\pm$ SEM) [95% CI 0.162, 3.370]. This corresponds to an overall relative reduction of 62%, compared to PBO slope of decline (-2.84 ± 0.57).
- [0237] When analyzing FVC in mL (adjusted for age, gender, and height, as measured by the difference in slope of the 60 mg arm [-47.2 ± 20.92] by the difference in slope of the PBO arm [-108.7 ± 20.58]), the 60 mg dose corresponds to a 61.4 ml relative treatment difference compared to PBO.
- [0238] Subgroup analyses of background SoC (SoC vs none) demonstrated favorable responses on the primary endpoint in the 60 mg group in contrast to the PBO group.
- [0239] Of those on background SoC (68% of the overall population), the 60 mg dose showed a treatment difference versus PBO on the primary endpoint (rate of change of ppFVC) of 1.41 ± 0.89 (mean $\pm$ SEM) [95% CI -0.341, 3.151], which corresponds to a 44% relative treatment benefit compared to PBO.
- [0240] Of those not on background SoC (32% of the overall population), the 60 mg dose showed a treatment difference versus PBO on the primary endpoint (rate of change of ppFVC) of 2.55 ± 1.73 (mean $\pm$ SEM) [95% CI -0.84, 5.948], which corresponds to a 123% relative treatment benefit compared to PBO.
- [0241] Subgroup analyses of participants enrolled while on stable background SoC (defined as either nintedanib or pirfenidone) (68% of the overall population) and those enrolled without being on SoC (No SoC; 32% of the overall population), showed favorable efficacy with 60 mg compared to PBO (Table 10).
- [0242] Subgroup analysis based on sex revealed differing rates of decline. Data not shown.

Table 9: Estimated difference in rate of decline from baseline to Week 26

	Primary Estimand ^a			Supplementary Estimand ^b		
ppFVC (%)	Population	Slope Difference (SE)	95% CI	Population	Slope Difference (SE)	95% CI

60 mg -PBO	Overall	1.45 (0.81)	-0.133, 3.028	Overall	1.77 (0.82)	0.162, 3.37
	SoC	1.22 (0.87)	-0.486, 2.929	SoC	1.41 (0.89)	-0.341, 3.151
	No SoC	2.01 (1.7)	-1.327, 5.355	No Soc	2.55 (1.73)	-0.84, 5.948
FVC (mL)	Slope Difference (SE) 95% CI			Slope Difference (SE) 95% CI		
60 mg-PBO	Overall	46.9 (29.14)	-10.3, 104.1	Overall	61.4 (29.35)	3.8, 119.0

CI = confidence interval; FVC = forced vital capacity; PBO = placebo; ppFVC = percent predicted forced vital capacity; SE = standard error; SoC = standard of care.

^a Under the primary estimand, all observations are used for the analysis regardless of dose reduction to 10 mg BID or matching PBO for meeting low BP criteria.

^b Under the supplementary estimand, all observations are used for analysis up to the time of dose reduction to 10 mg BID or matching PBO for meeting low BP criteria.

Table 10: Estimated Rate of Decline in ppFVC from Baseline to Week 26

Group	Primary Estimand			Supplementary Estimand		
	Population	Slope (SE)	95% C.I.	Population	Slope (SE)	95% C.I.
PBO	Overall	-2.67 (0.57)	-3.782, -1.565	Overall	-2.84 (0.57)	-3.968, -1.719
	SoC	-3.12 (0.61)	-4.321, -1.91	SoC	-3.18 (0.62)	-4.403, -1.951
	No SoC	-1.78 (1.18)	-4.093, 0.532	No SoC	-2.083 (1.21)	-4.454, 0.288
60 mg	Overall	-1.23 (0.57)	-2.353, -0.10	Overall	-1.08 (0.58)	-2.221, 0.067
	SoC	-1.89 (0.62)	-3.103, -0.686	SoC	-1.772 (0.63)	-3.015, -0.529
	No SoC	0.23 (1.23)	-2.178, 2.646	No SoC	0.471 (1.23)	-1.958, 2.899

[0243] Additional data for the IPF cohort is shown in FIGS. 8-10. As shown in FIG. 8, in the treatment policy strategy, the rate of change in ppFVC over 26 weeks in patients with IPF was -2.7% for placebo vs -2.8% and -1.2% for the 30-mg and 60-mg Compound A arms, respectively. The treatment difference between the 60-mg arm vs placebo was 1.4% (95% CI, -0.1 to 3.0), a relative reduction of 54% (FIG. 8A). Using the while-on-treatment strategy, the rate of change in ppFVC was -2.8% for placebo vs -3.2% and -1.1% for the 30-mg and 60-mg Compound A arms, respectively. The treatment difference between the 60-mg Compound A arm vs placebo was 1.8% (95% CI, 0.2 to 3.4), a 62% relative reduction (FIG. 8B). In the Bayesian analysis, the posterior probability of a positive treatment difference for 60-mg Compound A vs placebo was >95% under both estimand strategies.

[0244] Rate of change in FVC (mL) for the IPF cohort is shown in FIG. 9 while FIG. 10 shows the absolute change in FVC. The adjusted mean treatment difference in absolute change in FVC (mL) between the 60-mg Compound A and placebo arms at week 26 was 45.5 mL (FIG. 10A).

[0245] FIG. 11 shows the rate of change in ppFVC for subjects with and without background antifibrotic treatment in the IPF cohort. The treatment differences in rates of change in ppFVC were consistent between both groups (FIGS. 11A and 11B).

Efficacy Results Summary:

- The 30 mg dose group did not demonstrate efficacy compared to PBO in the overall population with and without SoC (data not shown).
- The 60 mg dose group demonstrated favorable treatment responses versus PBO in the overall population with and without SoC, and for the sub-group of participants on background SoC as well as for those not on SoC.
- These results indicate that Compound A has a favorable impact on FVC compared with PBO when used alone or on background therapy with nintedanib or pirfenidone.

[0246] In general, the overall adverse events among subjects with at least one TEAE were more frequently observed in the PBO group (Table 11). Discontinuations due to TEAE were evenly balanced across treatment groups (PBO: 9.8%; 30mg: 9.9%; 60 mg: 6.5%)

Table 11: Summary of Select Safety Data

Category, n (%)	PBO (N=92)	30 mg (N=91)	60 mg (N=93)	Active Total ^a
Subjects with at least one TEAE	74 (80.4)	69 (75.8)	69 (74.2)	138 (75.0)
Subjects with at least one AESI	19 (20.7)	18 (19.0)	9 (9.7)	27 (14.7)
Subjects with at least one TESAE	16 (17.4)	10 (11.0)	10 (10.8)	20 (10.9)
Subjects discontinuing study treatment due to a TEAE	9 (9.8)	9 (9.9)	6 (6.5)	15 (8.2)
Subjects with at least one TEAE related to the study treatment	20 (21.7)	23 (25.3)	25 (26.9)	48 (26.1)

Subjects who died due to a TEAE	2 (2.2)	3 (3.3)	4 (4.3)	7 (3.8)
Subjects who died	4 (4.4)	4 (4.4)	5 (5.4)	9 (4.9)

AESI = adverse event of special interest; PBO = placebo; TEAE = treatment emergent adverse event; TESAE = treatment emergent serious adverse event.

^a Active total includes both 30 mg and 60 mg groups

Safety Assessments:

- In general, overall safety events were more prevalent in the PBO groups.
- Treatment-emergent adverse event (TEAE):
 - PBO: 74 (80.4%); 30 mg: 69 (75.8%); 60 mg: 69 (74.2%)
- Adverse event of special interest (AESI):
 - PBO: 19 (20.7%); 30 mg: 18 (19.8%); 60 mg: 9 (9.7%)
- Treatment-emergent serious adverse event (TESAE):
 - PBO: 16 (17.4%); 30 mg: 10 (11.0%); 60 mg: 10 (10.8%)
- Discontinuations due to a TEAE:
 - PBO: 9 (9.8%); 30 mg: 9 (9.9%); 60 mg: 6 (6.5%)
- TEAE related to study treatment:
 - PBO: 20 (21.7%); 30 mg: 23 (25.3%); 60 mg: 25 (26.9%)
- No predominant system organ class or preferred term reported for treatment discontinuations
- Total deaths were 13:
 - PBO: 4 (4.4%); 30 mg: 4 (4.4%); 60 mg: 5 (5.4%).
 - Causes of death were: 9 due to disease progression; 3 due to pneumonia; 1 due to congestive heart failure.
- TEAE-related deaths: 9 (3.3%) participants of which occurred during the study or within 28 days of the last dose of treatment.
 - PBO: 2 (2.2%); 30 mg: 3 (3.3%); 60 mg: 4 (4.3%).
 - An additional 4 participants died beyond the 28-day TEAE window.

[0247] *Blood Pressure Monitoring:* Based on the pre-specified low BP safety monitoring and criteria specified in the protocol, those on 60 mg had the lowest frequencies of orthostatic intolerance, orthostatic hypotension, or pre-specified symptomatic or asymptomatic low BP criteria. In the overall population, the following

orthostatic intolerance, orthostatic hypotension, or the symptomatic or asymptomatic low BP events were observed:

- Orthostatic intolerance observed in 19 (6.9%) participants.
- PBO: 7 (7.6%); 30 mg: 10 (11.0%); 60 mg: 2 (2.2%)
- Orthostatic hypotension observed in asymptomatic low BP in 54 (19.6%) participants. Note that orthostatic hypotension is defined as a drop in SBP of ≥ 20 mmHg or DBP of ≥ 10 mmHg with an assumption of an upright posture from either supine or seated to upright position.
- PBO: 19 (20.7%); 30 mg: 21 (23.1%); 60 mg: 14 (15.1%)
- Orthostatic hypotension observed in symptomatic low BP in 21 (7.5%) participants.
- PBO: 7 (7.6%); 30 mg: 9 (9.9%); 60 mg: 5 (5.4%)
- Asymptomatic low blood pressure observed in 59 (21.4%) of participants.
- PBO: 20 (21.7%); 30 mg: 22 (24.2%); 60 mg: 17 (18.3%)
- Symptomatic low blood pressure observed in 27 (9.8%) participants.
- PBO: 10 (10.9%); 30 mg: 11 (12.1%); 60 mg: 6 (6.5%)
- Dose reductions to Compound A 10 mg BID vs. matching PBO were implemented due to protocol-defined low BP criteria (shown below) in 18 (6.5%) participants and approximately evenly distributed across arms.
- PBO: 5 (5.4%); 30 mg: 7 (7.7%); 60 mg: 6 (6.5%)

Asymptomatic blood pressure reduction criteria

[0248] Patient experiences any of the following, confirmed by retest within 15 minutes:

- Seated systolic blood pressure < 85 mmHg
- Seated diastolic blood pressure < 55 mmHg
- Orthostatic hypotension

Symptomatic blood pressure reduction criteria

[0249] Patient experiences symptoms that, in the investigator's opinion, could be associated with a reduction in blood pressure and also experiences at least one of the following, confirmed by retest within 15 minutes:

- Seated systolic blood pressure < 100 mmHg or seated diastolic blood pressure < 60 mmHg

- Decrease of seated systolic blood pressure of ≥ 20 mmHg from the previous visit or decrease of seated diastolic blood pressure of ≥ 10 mmHg from the previous visit
- Orthostatic hypotension
- Orthostatic tachycardia

[0250] Based on the pre-specified BP monitoring and low BP criteria in the protocol, these data demonstrate that the dose of Compound A 60 mg twice daily (BID), as compared to PBO, was not associated with any increased risk of orthostatic intolerance, orthostatic hypotension, orthostatic tachycardia, or symptomatic or asymptomatic low BP (Table 12). However, postdose reductions in SBP were observed with the 30 mg and 60 mg on Day 1 of dosing. The nadir post-dose mean reductions from baseline in sitting SBP were noted at 2 hours post-dose (PBO: -2.1 mmHg; Compound A 30 mg: -10.5 mmHg; Compound A 60 mg: -14.1 mmHg). These reductions were not associated with any clinical sequelae and were self-limited in nature.

Table 12: Summary of Low Blood Pressure Data

Category, n (%)	PBO (N=92)	30 mg (N=91)	60 mg (N=93)	Total
Orthostatic Intolerance	7 (7.6)	10 (11.0)	2 (2.2)	19 (6.9)
Asymptomatic low blood pressure	20 (21.7)	22 (24.2)	17 (18.3)	59 (21.4)
Orthostatic hypotension*	19 (20.7)	21 (23.1)	14 (15.1)	54 (19.6)
Symptomatic low blood pressure	10 (10.9)	11 (12.1)	6 (6.5)	27 (9.8)
Orthostatic hypotension*	7 (7.6)	9 (9.9)	5 (5.4)	21 (7.6)

PBO = placebo

* Orthostatic hypotension is defined as a drop in SBP of ≥ 20 mmHg or DBP of ≥ 10 mmHg with an assumption of an upright posture from either supine or seated to upright position.

- [0251] The number of dose reductions (and percent of the total subjects in the group) in the IPF cohort were: 5 (5.4) for placebo; 7 (7.7) for 30 mg Compound A; and 6 (6.5) for 60 mg of Compound A.

EXAMPLE 4B: PPF Cohort

- [0252] A total of 123 participants with PPF were randomized. Participants (age ≥ 21 years) were randomized (1:1:1) to receive 30 mg or 60 mg Compound A or PBO twice daily for 26 weeks. Subjects with a centrally read HRCT obtained at screening demonstrating evidence of $> 10\%$ parenchymal fibrosis within the whole lung along with:

(a) evidence of ILD progression within the 24 months before screening, defined as either: a decline in the relative ppFVC of $\geq 10\%$, or a decline in the relative ppFVC of $\geq 5\%$ to $< 10\%$ along with increased extent of fibrosis on pre-screening thoracic computed tomography compared with prior imaging, or symptoms associated with progression of ILD along with an increased extent of fibrosis on pre-screening thoracic computed tomography compared with prior imaging;

(b) interstitial lung diseases of diverse etiologies, excluding connective tissue disease – associated interstitial lung disease (except rheumatoid arthritis-associated interstitial lung disease) and sarcoid; were enrolled. Immunosuppressive medications (mycophenolate mofetil, mycophenolic acid, azathioprine and/or tacrolimus) were permitted only if dosing is stable for ≥ 6 months prior to screening. If receiving antifibrotic agents pirfenidone or nintedanib, patients had to receive a stable dosage for ≥ 3 months prior to screening and during the screening period; if not receiving pirfenidone or nintedanib, patients had to be naive to both drugs or not have received either 4 weeks prior to Day 1. A total of 47 (38.2%) subjects were receiving antifibrotic treatment (with or without immunosuppression therapy). Of those subjects, 34 were being treated with nintedanib and 13 with pirfenidone. Participants were stratified by usual interstitial pneumonia (UIP) pattern (presence versus absence) and background therapy (antifibrotics +/- ILD-targeted immunosuppression versus ILD-targeted immunosuppression alone versus none). UIP pattern was present in 52% of subjects and unclassifiable ILD was the most common disease categorization.

[0253] The study was not powered to detect statistical significance (no formal testing). No target effect size was defined in the study design. There were two estimand approaches for analysis:

Treatment Policy: Effect of treatment with dose reduction as part of treatment regimen.

While-On Treatment: Effect of treatment without dose reduction.

[0254] Of the 123 treated participants that contributed to these analyses, 90.2% (n=111) completed the 26-week treatment phase and 9.8% (n=12) were treatment discontinued (6 (4.9%) were discontinued for adverse events). Treatment discontinuations across treatment groups (PBO: 17.1%; 30 mg: 7.5%; 60 mg: 4.8%). A total of 91 (74%) subjects continued into a 26 Week Optional Treatment Extension (OTE).

[0255] The main efficacy endpoint, rate of FVC decline (in % of predicted) from baseline to wk-26 in the PPF cohort, was estimated using a linear mixed-effects model utilizing all FVC timepoints. It was analyzed under a primary estimand (utilizing all data, treatment policy strategy), and under supplementary estimand (utilizing all data up to the point of dose reduction, while-on-treatment strategy). Analysis was performed in the overall population as well as in sub-groups by 1) background anti-fibrotic treatment or not 2) UIP radiographic pattern (presence or not). The mean baseline ppFVC was 66.7% for the PPF cohort.

[0256] Table 13 shows the baseline demographics and clinical characteristics of subjects in the PPF cohort while Table 14 shows their baseline disease characteristics.

Table 13: Baseline Demographics and Clinical Characteristics

Parameter*	PPF Cohort		
	Placebo (n=41)	30-mg Compound A (n=40)	60-mg Compound A (n=42)
<i>Demographics</i>			
Age, years	68.8±8.1	71.4±7.9	67.9±8.4
Male sex, no. (%)	20 (48.8)	23 (57.5)	22 (52.4)
Race, no. (%)			
White	31 (75.6)	27 (67.5)	32 (76.2)
Asian	8 (19.5)	9 (22.5)	6 (14.3)
Other	2 (4.9)	4 (10.0)	4 (9.5)
<i>Clinical characteristics</i>			
Weight, kg	71.9±16.2	73.5±17.3	74.9±19.4
BMI, kg/m ²	26.9±4.7	26.3±5.0	27.0±4.8

Cigarette smoking history, no. (%)			
Never	19 (46.3)	19 (47.5)	24 (57.1)
Current	0	0	0
Former	22 (53.7)	21 (52.5)	18 (42.9)
Concurrent background treatment [†] , no. (%)			
Pirfenidone	3 (7.3)	4 (10.0)	6 (14.3)
Nintedanib	14 (34.1)	11 (27.5)	9 (21.4)
None	20 (48.8)	22 (55.0)	24 (57.1)
Time since diagnosis, years	2.8±2.6	3.1±2.7	3.9±2.7
No.	39	36	39
FVC, mL	2126±616	2246±728	2113±723
FVC, percent of predicted	68±18	67±16	65±17
No.	26	30	32
DLco, percent of predicted, hemoglobin-corrected	43.4±13.0	45.7±14.6	46.4±12.9
No.	36	36	38
6MWT, meters	344.8±109.6	345.3±109.1	352.9±103.7
No.	39	39	42
Quantitative lung fibrosis (HRCT), %	18.1±11.1	19.1±11.9	23.9±12.4

*Values before and after plus-minus symbols represent means ± SD. [†]Patients with PPF were permitted to remain on background antifibrotics ± ILD-targeted immunosuppressants (see Supplementary Table S1). 6MWT, 6-minute walk test; BMI, body mass index; DLco, diffusing capacity of the lung for carbon monoxide; FVC, forced vital capacity; HRCT, high-resolution computed tomography; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; PPF, progressive pulmonary fibrosis; SD, standard deviation.

Table 14. Baseline Disease Characteristics for the PPF Cohort

Parameter, no. (%)	Placebo (n=41)	30-mg Compound A (n=40)	60-mg Compound A (n=42)
UIP pattern present	21 (51.2)	22 (55.0)	21 (50.0)
<i>Disease classification</i>			
Unclassifiable ILD	11 (26.8)	13 (32.5)	9 (21.4)
Rheumatoid arthritis ILD	10 (24.4)	4 (10.0)	6 (14.3)
Chronic hypersensitivity pneumonitis	8 (19.5)	6 (15.0)	7 (16.7)
Idiopathic fibrotic NSIP	3 (7.3)	7 (17.5)	6 (14.3)
Interstitial pneumonia with autoimmune features	4 (9.8)	2 (5.0)	6 (14.3)
Other progressive ILD	5 (12.2)	8 (20.0)	8 (19.0)

<i>Concurrent background treatment</i>			
Antifibrotics without ILD-targeted immunosuppressants	15 (36.6)	13 (32.5)	13 (31.0)
ILD-targeted immunosuppressants without antifibrotics	4 (9.8)	3 (7.5)	3 (7.1)
Antifibrotic + ILD-targeted immunosuppressants	2 (4.9)	2 (5.0)	2 (4.8)
No background treatment	20 (48.8)	22 (55.0)	24 (57.1)

ILD, interstitial lung disease; NSIP, non-specific interstitial pneumonia; PPF, progressive pulmonary fibrosis; UIP, usual interstitial pneumonia.

[0257] Summary results are described in Tables 15-26; and additional results from the final analysis from the PPF cohort are described below.

Table 15: Estimated Difference in Rate of Decline in ppFVC from Baseline to Week 26 in Different Subgroups

Population	Treatment difference 60 mg v placebo	N (60 mg /placebo)	95% CI	Relative Reduction
Overall	2.94	42/41	0.35 to 5.53	69%
UIP subgroup	2.12	21/21	-1.06 to 5.31	54%
Non UIP subgroup	3.80	21/20	-0.48 to 8.09	84%
Anti-fibrotic subgroup	3.28	15/15	-1.1 to 7.66	75%
No antifibrotic subgroup	2.61	27/26	-0.6 to 5.82	63%

- Efficacy of Compound A (60 mg) was shown in a population in which 37% of patients were on background anti-fibrotics.
- 60 mg relative reduction in PPF cohort (69%) was similar to IPF cohort (62%)
- Clear dose response
- Efficacy consistent in all sub-groups, i.e., irrespective of background antifibrotics or of UIP pattern.

Table 16: Main Analysis in FVC (% Predicted): Rate of Decline in Overall Population – Primary Estimand – Treatment Policy Strategy (Relative Reduction = 74%)

Treatment	Slope (S.E.)	Difference	Difference (S.E.)	95% C.I.
Placebo (n=41)	-4.27 (0.93)			
30 mg (n=39)	-2.7 (0.9)	30 mg – placebo	1.57 (1.29)	[-0.97, 4.11]
60 mg (n=42)	-1.11 (0.86)	60 mg - placebo	3.15 (1.27)	[0.66, 5.64]

Table 17: Main Analysis in FVC (% Predicted): Rate of Decline in Overall Population – Supplementary Estimand – While On Treatment (Relative Reduction = 69.3%)

Treatment	Slope (S.E.)	Difference	Difference (S.E.)	95% C.I.
Placebo (n=41)	-4.24 (0.94)			
30 mg (n=39)	-2.45 (0.96)	30 mg – placebo	1.78 (1.34)	[-0.86, 4.43]
60 mg (n=42)	-1.3 (0.92)	60 mg - placebo	2.94 (1.32)	[0.35, 5.53]

[0258] Additional data for the PPF cohort is shown in FIGS. 8-18. As shown in FIG. 8, the rate of change in ppFVC over 26 weeks in patients with PPF was -4.3% for placebo vs -2.7% and -1.1% for the 30-mg and 60-mg Compound A arms, respectively, per the treatment policy strategy. The treatment difference for 60-mg Compound A vs placebo was 3.2% (95% CI, 0.7 to 5.6), a relative reduction of 74% (FIG. 8C). Using the while-on-treatment strategy, the rate of change in ppFVC was -4.2% for placebo vs -2.5% and -1.3% for the 30-mg and 60-mg arms, respectively. The treatment difference between 60-mg Compound A vs placebo was 2.9% (95% CI, 0.4 to 5.5), a relative reduction of 69% (FIG. 8D).

[0259] Rate of change in FVC (mL) for the PPF cohort is shown in FIG. 9 while FIG. 10 shows the absolute change in FVC. The adjusted mean treatment differences in absolute

change in FVC (mL) between the 60-mg Compound A and placebo arms at week 26 was 87.4 mL (FIG. 10B).

[0260] FIGS. 12 and 13 show the mean observed change from baseline to week 26 in ppFVC percentage and FVC in the PPF cohort. As shown in the figures, both 30 mg and 60 mg show improvement over placebo at week 8, but 30 mg shows more significant improvement after week 20 while 60 mg maintains the improvement over placebo through the end of week 26.

Table 18: Subgroup Analysis in FVC (% Predicted): Rate of Decline in UIP Present Subjects – Primary Estimand – Treatment Policy Strategy (Relative Reduction = 63%)

Treatment	Slope (S.E.)	Difference	Difference (S.E.)	95% C.I.
Placebo (n=21)	-3.95 (1.18)			
30 mg (n=22)	-3.07 (1.09)	30 mg – placebo	0.88 (1.6)	[-2.28, 4.04]
60 mg (n=21)	-1.46 (1.1)	60 mg - placebo	2.49 (1.61)	[-0.68, 5.67]

Table 19: Subgroup Analysis in FVC (% Predicted): Rate of Decline in UIP Absent Subjects – Primary Estimand – Treatment Policy Strategy (Relative Reduction = 83.6%)

Treatment	Slope (S.E.)	Difference	Difference (S.E.)	95% C.I.
Placebo (n=20)	-4.56 (1.48)			
30 mg (n=17)	-2.31 (1.53)	30 mg – placebo	2.25 (2.13)	[-1.95, 6.44]
60 mg (n=21)	-0.75 (1.38)	60 mg - placebo	3.81 (2.02)	[-0.18, 7.79]

Table 20: Subgroup Analysis in FVC (% Predicted): Rate of Decline in UIP Present Subjects – Supplementary Estimand – While on Treatment (Relative Reduction = 54%)

Treatment	Slope (S.E.)	Difference	Difference (S.E.)	95% C.I.

Placebo (n=21)	-3.94 (1.16)			
30 mg (n=22)	-2.66 (1.12)	30 mg – placebo	1.28 (1.61)	[-1.89, 4.46]
60 mg (n=21)	-1.82 (1.12)	60 mg - placebo	2.12 (1.62)	[-1.06, 5.31]

Table 21: Subgroup Analysis in FVC (% Predicted): Rate of Decline in UIP Absent Subjects –
Supplementary Estimand – While on Treatment (Relative Reduction = 84.4%)

Treatment	Slope (S.E.)	Difference	Difference (S.E.)	95% C.I.
Placebo (n=20)	-4.5 (1.55)			
30 mg (n=17)	-2.24 (1.68)	30 mg – placebo	2.26 (2.28)	[-2.24, 6.77]
60 mg (n=21)	-0.7 (1.53)	60 mg - placebo	3.8 (2.17)	[-0.48, 8.09]

[0261] FIGS. 14 and 15 show the mean observed change from baseline to week 26 in ppFVC percentage and FVC in patients with and without UIP within the PPF cohort while FIG. 16 shows the rate of change in ppFVC in PPF patients with and without UIP. As shown in the figures, treatment differences were seen in the PPF cohort independent of UIP pattern presence or absence. Acute exacerbations of lung fibrosis were observed in 6 patients (2%) with IPF (placebo: n=2; 30-mg: n=3; 60-mg: n=1) and in 3 patients (2%) with PPF, all in the placebo arm.

Table 22: Subgroup Analysis in FVC (% Predicted): Rate of Decline in Subjects Receiving Antifibrotic Treatment – Primary Estimand – Treatment Policy (Relative Reduction = 85%)

Treatment	Slope (S.E.)	Difference	Difference (S.E.)	95% C.I.
Placebo (n=15)	-4.42 (1.55)			
30 mg (n=14)	-2.43 (1.44)	30 mg – placebo	1.99 (2.12)	[-2.19, 6.18]

60 mg (n=15)	-0.68 (1.37)	60 mg - placebo	3.74 (2.1)	[-0.35, 7.83]
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Table 23: Subgroup Analysis in FVC (% Predicted): Rate of Decline in Subjects Not Receiving Antifibrotic Treatment – Primary Estimand – Treatment Policy (Relative Reduction = 68.5%)

Treatment	Slope (S.E.)	Difference	Difference (S.E.)	95% C.I.
Placebo (n=26)	-4.16 (1.15)			
30 mg (n=25)	-2.88 (1.15)	30 mg – placebo	1.28 (1.63)	[-1.93, 4.5]
60 mg (n=27)	-1.31 (1.11)	60 mg - placebo	2.85 (1.6)	[-0.3, 6.01]

Table 24: Subgroup Analysis in FVC (% Predicted):
Rate of Decline in Subjects Receiving Antifibrotic Treatment – Supplementary Estimand –
While on Treatment (Relative Reduction = 74.9%)

Treatment	Slope (S.E.)	Difference	Difference (S.E.)	95% C.I.
Placebo (n=15)	-4.38 (1.61)			
30 mg (n=14)	-1.8 (1.58)	30 mg – placebo	2.58 (2.25)	[-1.87, 7.03]
60 mg (n=15)	-1.1 (1.53)	60 mg - placebo	3.28 (2.21)	[-1.1, 7.66]

Table 25: Subgroup Analysis in FVC (% Predicted):
Rate of Decline in Subjects Not Receiving Antifibrotic Treatment – Supplementary Estimand –
While on Treatment (Relative Reduction = 62.6%)

Treatment	Slope (S.E.)	Difference	Difference (S.E.)	95% C.I.
Placebo (n=26)	-4.17 (1.16)			

30 mg (n=25)	-2.83 (1.2)	30 mg – placebo	1.34 (1.66)	[-1.94, 4.61]
60 mg (n=27T)	-1.56 (1.15)	60 mg - placebo	2.61(1.63)	[-0.6, 5.82]

[0262] FIGS. 17 and 18 show the mean observed change from baseline to week 26 in ppFVC percentage and FVC in patients with and without additional antifibrotic treatment within the PPF cohort, while FIG. 11 shows the rate of change in ppFVC for subjects with and without background antifibrotic treatment in the PPF cohort. The treatment differences in rates of change in ppFVC were consistent with or without background antifibrotic use PPF cohorts (FIGS. 11C and 11D).

Table 26: Summary of Select Safety Data

Patients, no. (%)	Placebo (n=41)	30 mg Compound A (n=40)	60 mg Compound A (n=42)
≥1 TEAE	32 (78.0)	33 (82.5)	28 (66.7)
≥1 TEAE related to study drug	7 (17.1)	7 (17.5)	11 (26.2)
≥1 TESAЕ	13 (31.7)	4 (10.0)	5 (11.9)
Discontinuations due to TEAEs	6 (14.6)	1 (2.5)	0
Deaths due to TEAEs	3 (7.3)	0	0
Diarrhea	6 (14.6)	6 (15.0)	3 (7.1)
Cough	4 (9.8)	3 (7.5)	5 (11.9)
COVID-19	2 (4.9)	6 (15.0)	6 (14.3)
Orthostatic hypotension	1 (2.4)	2 (5.0)	4 (9.5)
Dyspnea	6 (14.6)	2 (5.0)	0
Nausea	3 (7.3)	4 (10.0)	1 (2.4)

Dizziness	4 (9.8)	0	4 (9.5)
Hypotension	0	4 (10.0)	3 (7.1)
Hypertension	0	0	1 (2.4)
Vomiting	1 (2.4)	3 (7.5)	0
Rash	0	3 (7.5)	0

COVID-19, coronavirus disease of 2019; IPF, idiopathic pulmonary fibrosis; PPF, progressive pulmonary fibrosis; TEAE, treatment-emergent adverse event; TESAE, treatment-emergent serious adverse event.

Summary of Adverse Events

[0263] Subjects with at least one treatment emergent adverse event (TEAE): PBO-24%, 30mg-10%, 60mg-24%

- Subjects with at least one treatment emergent serious adverse event (TESAE): PBO-32%, 30 mg-10%, 60 mg-12%
- Subjects with at least one TEAE due to investigative medicinal product (IMP): PBO-17%, 30 mg-18%, 60 mg-26%
- Seven subjects had an adverse ending leading to treatment discontinuation
 - 6 were in the PBO group and 1 was in the 30 mg dose group (due to hypotension)
- Three subjects died due to a TEAE; all 3 were in the PBO group
 - 1 infectious pneumonia, 1 PE, 1 respiratory failure
- Dose dependent BP findings reaffirm low BP safety risk with Compound A
 - Day 1 post-dose reductions in blood pressure; without clinical consequences
 - Dose dependent low BP thresholds ("events"): PBO-24%, 30mg-30%, 60mg-41%
 - Dose reductions: PBO-2%, 30mg-15%, 60mg-12%
 - AESI due to low BP: PBO-24%, 30mg-10%, 60mg-24%
- No notable imbalances in marked laboratory abnormalities among treatment groups
- No hepatobiliary toxicity

[0264] In patients with PPF, the nadir postdose reductions from baseline on day 1 in mean seated systolic blood pressure were –4.2 mmHg, –10.7 mmHg, and –12.7 mmHg for the placebo, 30 mg, and 60 mg Compound A arms, respectively. Prespecified blood pressure reduction criteria (shown below) increased in a dose-dependent manner across PPF cohort arms (Table 27).

Asymptomatic blood pressure reduction criteria

[0265] Patient is experiencing any of the following, confirmed by retest within 15 minutes:

- Seated systolic blood pressure <85 mmHg
- Seated diastolic blood pressure <55 mmHg
- Orthostatic hypotension

Symptomatic blood pressure reduction criteria

[0266] Patient is experiencing symptoms that, in the investigator's opinion, could be associated with a reduction in blood pressure and is also experiencing at least one of the following, confirmed by retest within 15 minutes:

- Seated systolic blood pressure <100 mmHg or seated diastolic blood pressure <60 mmHg
- Decrease of seated systolic blood pressure of ≥ 20 mmHg from the previous visit or decrease of seated diastolic blood pressure of ≥ 10 mmHg from the previous visit
- Orthostatic hypotension
- Orthostatic tachycardia

Table 27: Summary of Prespecified Asymptomatic or Symptomatic Blood Pressure Reduction Criteria and Dose Reductions

	PPF Cohort		
	Placebo (n=41)	30-mg Compound A (n=40)	60-mg Compound A (n=42)
Patients, no. (%)			
Asymptomatic blood pressure reduction*	6 (14.6)	9 (22.5)	13 (31.0)

Orthostatic hypotension [†]	6 (14.6)	6 (15.0)	11 (26.2)
Symptomatic blood pressure reduction*	2 (4.9)	2 (5.0)	6 (14.3)
Orthostatic hypotension [†]	1 (2.4)	1 (2.5)	4 (9.5)
Dose reductions	1 (2.4)	6 (15.0)	5 (11.9)

*The prespecified criteria that define asymptomatic versus symptomatic blood pressure reduction are shown in the Supplementary Methods. [†]Orthostatic hypotension was defined as a drop in systolic blood pressure of ≥ 20 mmHg or diastolic blood pressure of ≥ 10 mmHg with an assumption of an upright posture from either supine or seated to upright position. IPF, idiopathic pulmonary fibrosis; PPF, progressive pulmonary fibrosis.

[0267] Compound A was well-tolerated, demonstrated no unexpected safety findings, and had an overall profile similar to that seen in the IPF cohort. Other than low blood pressure, the adverse event profile was generally in favor of the 60 mg group versus placebo.

[0268] There was a dose dependent day-1 blood pressure reduction in the PPF cohort, similar in magnitude to what was seen in the IPF cohort. Orthostatic hypotension (asymptomatic and symptomatic) was higher in the 60 mg group than for other groups. There were 2 cases of syncope and 1 case of presyncope, but all were in the placebo group.

EXAMPLE 5: A Multicenter, Randomized, Double-blind, Placebo-controlled, Phase 3 study to evaluate the Efficacy, Safety, and Tolerability of Compound A in Participants with Progressive Pulmonary Fibrosis (PPF).

Scientific Rationale for Study Design

Rationale for the Titration Phase:

[0269] Reductions in BP were noted with first dose administration of Compound A at 30 or 60 mg twice daily (BID) in the Phase 2 study and at the same as well as higher doses in Phase 1 studies. PK/PD modeling and simulation (based on Phase 1 and Phase 2 blood pressure results) suggests that Day 1 post-dose reductions in BP observed in the study may be mitigated by dose titration. Therefore, a dose titration plan is being implemented

with BP monitoring for safety and to evaluate the impact of dose titration on BP and clinical events related to low BP.

Rationale for the Study Design:

- [0270] The primary endpoint of Cohort 1 is the number of spontaneous syncopal episodes that occur in the Compound A >60 mg and PBO arms after the first dose of Compound A >60 mg until the Week 4 visit. In the Phase 2 study, no syncope events occurred in the Compound A 30 and 60 mg arms. Post-dose reductions in SBP were observed in these arms on Day 1 of dosing and these reductions were self-limited and not associated with any clinical sequelae. Spontaneous syncope is a clinically meaningful indicator of hypotension and will be monitored and reviewed in Cohort 1 of the study to enable the decision to proceed with the Compound A >60 mg dose.
- [0271] The primary endpoint chosen for Cohort 2 in this Phase 3 study is similar to that in other IPF and PPF trials for approved therapies. The Phase 3 pirfenidone and nintedanib IPF trials demonstrated benefits on FVC in patients receiving active treatment, compared with PBO, after 72 weeks and 52 weeks of treatment, respectively. Furthermore, a 10% or greater absolute reduction in FVC over a 6-month period has been shown to be associated with an almost five-fold increase in the risk of death over the subsequent 1-year period. A decline in FVC of only 10% was also predictive, with a greater than two-fold increased risk of death over the subsequent year. Collectively, it has been established that FVC represents a robust clinical measurement that is a standard for the determination of progression of disease whereby categorical decrements of FVC are powerful predictors of mortality.
- [0272] The secondary endpoints chosen for Cohort 2 in this Phase 3 study are similar to those in other IPF and PPF trials and well suited to reliably assess efficacy and safety. This Phase 3 study will extend the placebo-controlled phase beyond 52 weeks to increase the likelihood of demonstrating that Compound A demonstrates clinically meaningful benefits beyond FVC, for example, lung fibrosis-related hospitalization, acute exacerbations, patient-reported outcomes (PRO) data, potentially even survival, adverse events (AEs), significant adverse events (SAEs), and other safety assessments.
- [0273] Given the extension of the placebo-controlled period beyond 52 weeks, and that this participant population may require emergency care, disease worsening criteria have been incorporated into the study, participants that have disproportionate declines in FVC

over time or who experience acute exacerbations or hospitalization related to lung fibrosis progression will be able to transition to double-blind active investigational therapy.

STUDY POPULATION

Key Inclusion Criteria

- [0274]** Participants are eligible to be included in the study if all the following criteria apply:
- 1) ≥ 21 years of age at the time of signing the informed consent form (ICF).
 - 2) A clinical diagnosis of ILD and one of the following PPF progression criteria:
 - a) *Imaging and Evidence of Previous Progression by FVC and/or symptoms:* Centrally read HRCT that has $>10\%$ parenchymal fibrosis within the whole lung at screening and features consistent with progressive ILD within 24 months prior to screening, defined as:
 - i) a decline in the relative ppFVC of $\geq 10\%$, or
 - ii) a decline in the relative ppFVC of $\geq 5\%$ to $<10\%$ and an increased extent of fibrosis on pre-screening thoracic computed tomography compared with prior imaging, or
 - iii) decline in relative ppFVC of $\geq 5\%$ to $<10\%$ and symptoms associated with progression of ILD, or
 - iv) symptoms associated with progression of ILD and an increased extent of fibrosis on pre-screening thoracic computed tomography compared with prior imaging.
 - 3) Percent Predicted Forced Vital Capacity (ppFVC) $\geq 40\%$.
 - 4) Forced expiratory volume in 1 second (FEV1)/FVC ≥ 0.7 .
 - 5) Single-breath, hemoglobin-corrected, percent predicted diffusion capacity of the lung for carbon monoxide (DLCO) $\geq 25\%$.
 - 6) If on pirfenidone or nintedanib, participants must have been receiving a stable dose for at least 3 months (90 days) prior to screening, during the screening period and up to randomization (Day 1).
 - 7) If not currently on pirfenidone or nintedanib, participants must not have received either of these medications within 4 weeks prior to screening.

- 8) Participants with rheumatoid arthritis-ILD. Participants with sarcoidosis and other CTD-ILDs will be allowed upon DMC recommendation after the first safety review..
- 9) Women who are of childbearing potential must have a highly effective form of contraception (if hormonal method is used, a barrier method must also be used).
 - a) Negative pregnancy serum test prior to Day 1 and negative pregnancy urine/serum test on Day 1, prior to study treatment administration.
- 10) Men who are sexually active with WOCBP agree to use male barrier contraception.

[0275] A study with PPF will be randomized to receive Compound A at 60 mg or higher or matching placebo orally twice daily (BID) at a ratio of 1:1:1. Approximately equal number of participants will be randomized to each treatment arm. Stable, background anti-fibrotic therapy with nintedanib or pirfenidone will be allowed. Similarly, select background immunosuppressive therapies targeting ILD will be allowed. The study will utilize a 2-cohort design:

[0276] Cohort 1 is a single-blind design. The study team, investigators, participants and families are blinded to participant-level treatment assignments, whereas an internal review committee (IRC) will be unblinded to all Cohort 1 data. Cohort 1 will enroll approximately 60 participants with PPF to evaluate the safety and tolerability of Compound A. During the first 4 weeks of treatment, the IRC will closely monitor the occurrence of any spontaneous syncopal events in the Compound A >60 mg treatment arm in both Phase 3 studies. These episodes are defined as a clinical syndrome in which transient loss of consciousness is caused by a period of inadequate cerebral blood flow and oxygenation, most often the result of an abrupt drop of systemic BP, associated with spontaneous recovery in a participant without medical history of syncope. Upon review of all available data, the IRC will determine one of the following decisions:

- To continue Cohort 1 without modification (fewer than 2 spontaneous syncopal events without plausible alternative etiology in the Compound A >60 mg arm compared with PBO, and without an undesirable safety profile compared with PBO occurring in Cohort 1 from this study or the IPF study; assessment will be performed by the IRC) and initiate with Compound A 60 mg, >60 mg, and PBO arms in Cohort 2

OR

- To terminate the Compound A >60 mg arm in Cohort 1 (2 or more spontaneous syncopal events without plausible alternative etiology in the Compound A >60 mg arm compared with PBO, or with an undesirable safety profile compared with PBO occurring in Cohort 1 from this study or the IPF study; assessment will be performed by the IRC). All participants in the Compound A >60 mg arm in Cohort 1 will complete an early termination visit, and will be encouraged to complete a safety follow-up visit approximately 28 days after the last dose of Investigational Medicinal Product (IMP). Participants in Cohort 1 in the blinded Compound A 60 mg or PBO arms will continue in Cohort 1 through end of study (EOS). If the IRC determines that the Compound A >60 mg arm is discontinued in Cohort 1, then this dose will not be initiated in Cohort 2, and Cohort 2 will only include the Compound 60 mg and PBO arms.

[0277] Cohort 2 will subsequently enroll participants with PPF based on IRC evaluation of spontaneous syncopal events occurring in Cohort 1 from either PPF or IPF studies, whichever completes enrollment first.

[0278] Cohort 2 is a registrational, double-blind design, whereby Sponsor, investigators, participants and families will remain blinded to treatment assignments. Cohort 2 will investigate the efficacy, safety, and tolerability of Compound A compared with PBO. Treatment arms in Cohort 2 will be determined by the outcome of the IRC review of Cohort 1 data and will result in one of the following options:

- Three treatment arms: Approximately 1032 participants with PPF will be randomized 1:1:1 to Compound A 60 mg, >60 mg, or PBO, BID

OR

- Two treatment arms: Approximately 688 participants with PPF will be randomized 1:1 to Compound A 60 mg or PBO, BID

Screening period (Up to 6 weeks)

[0279] *Treatment period* Treatment period is approximately 4 years from the Day 1 visit for the first randomized participant in Cohort 1 through the last participant's end of treatment (EOT) visit in Cohort 2 (a participant's individual study duration could be from a minimum of 52 weeks up to approximately 4 years depending on when last participant completes the Week 52 visit endpoint):

Day 1 until Week 52 visit

- [0280] Titration period: Day 1 (day of first dose of IMP) up to Day 16 with a minimum of 2 consecutive days of dosing required between titration visits. If any low BP criteria are met during titration, participants must either be rechallenged at the next visit or discontinue treatment

Post-titration period until EOT

- [0281] EOT is defined as when the last participant completes their last scheduled treatment visit as per the Schedule of Activities. The EOT visit for the last participant is defined as completion of Week 52 visit. The EOT visit is triggered for all participants on treatment when the date of the projected Week 52 visit is known for the last participant . The primary endpoint is captured at Week 52.
- [0282] The last participant is defined as the participant to complete the safety follow-up visit last.
- [0283] *Post-treatment safety follow-up (SFU) period (28 days following the last dose of IMP)*

OBJECTIVES AND ENDPOINTS

- [0284] The primary objective of Cohort 1 is to assess the safety of the Compound A >60 mg BID dose through the Week 4 visit. The primary endpoint of Cohort 1 is the number of spontaneous syncopal episodes that occur in the Compound A and PBO arms during the period that starts with the first dose of Compound A and ends with the Week 4 visit.
- [0285] The secondary objective of Cohort 1 is to assess the safety and tolerability of Compound A 60 and >60 mg BID, compared with PBO, through end of study. The secondary endpoints include the discontinuation rate due to any AE related to low BP and safety assessments of Compound A 60 mg and >60 mg compared with PBO through EOS.
- [0286] Cohort 2 primary, key secondary, secondary, and exploratory objectives are shown below:

Primary Objectives and Endpoints for Cohort 2

Objectives	Endpoints
Primary To evaluate the efficacy of two doses of Compound A, 60 mg and a dose higher than 60 mg twice daily (BID), compared to matching placebo (PBO), demonstrating improvement in absolute change in FVC from baseline to Week 52 in participants with PPF.	Primary Absolute change in FVC (mL) from baseline to Week 52
Key Secondary - To evaluate the effect of Compound A 60 and >60 mg BID, compared with PBO, on disease progression from baseline through EOS^a - To evaluate the effect of Compound A 60 and >60 BID, compared with PBO, on quality of life and morbidity from baseline to Week 52.	Key Secondary □ Disease progression 4-component composite endpoint: Time to first disease progression event in at least 1 of the following, from Day 1 through EOS: -Absolute ppFVC decline of $\geq 10\%$ from baseline -Acute exacerbation of pulmonary fibrosis^b -Respiratory-related hospitalization -All-cause mortality └ Change in L-PF cough domain score from baseline at Week 52 (key secondary endpoint in non-EU health authority submission only) └ Change in L-PF dyspnea domain score from baseline at Week 52 (key secondary endpoint in non-EU health authority submission only) □ Change in walking distance measured in 6MWT from baseline at Week 52
Secondary - To evaluate the treatment effect of 2 doses of Compound A, 60 and >60 mg BID, compared with PBO, on - Selected clinical assessments from baseline to Week 52 - Disease progression events from baseline up to EOS^a	Secondary - Time to first occurrence of at least 1 of the following events, from baseline through EOS: - Acute exacerbation of pulmonary fibrosis^b - Respiratory-related hospitalization - All-cause mortality - Time to absolute ppFVC decline of $\geq 10\%$ from Day 1 through EOS - Time to first acute exacerbation of pulmonary fibrosis from Day 1 through EOS - Time to first respiratory-related hospitalization from Day 1 through EOS - Time to all-cause mortality from Day 1 through EOS - Changes in remaining L-PF fatigue domain and impact module score from baseline at Week 52 - Changes in Cough NRS from baseline at Week 52 - Changes in EQ-5D-5L health utility index scores and visual analog scale scores from baseline at Week 52 - Rate of decline in FVC (mL) from baseline at Week 52 - Rate of decline in ppFVC (%) from baseline at Week 52

	• Change in ppFVC from baseline at Week 52 • Proportion of participants with absolute decline in ppFVC $\geq 10\%$ at Week 52 • Proportion of participants with relative decline in ppFVC $\geq 10\%$ at Week 52 • Change in L-PF cough domain score from baseline at Week 52 (secondary endpoint in EU only) • Change in L-PF dyspnea domain score from baseline at Week 52 (secondary endpoint in EU only) • Change in DLCO SB (mL/min/mm Hg) (corrected for hemoglobin) from baseline at Week 52 • Change in ppDLCO SB (%) (corrected for hemoglobin) from baseline at Week 52 • Change in the QLF score via HRCT from baseline at Week 52
Objectives	Endpoints
• To explore the trend of the patient-reported symptoms, impact of the disease, and overall health status over the duration of the study	• Changes from baseline to EOS in: – Patient-reported symptoms and impacts of the disease as assessed by the L-PF cough, dyspnea, and fatigue domain scores, and impacts module scores • Cough NRS
Secondary	Secondary
• To evaluate the safety and tolerability of Compound A in participants with PPF randomized to receive Compound A at 60 or >60 mg BID, compared with PBO, through Week 52 and up to EOS.	• AEs • SAEs • AEs leading to early discontinuation of IMP • Treatment-emergent deaths • Clinical laboratory findings • ECGs • Vital signs

Abbreviations: AE, adverse event; BID, twice daily; DLCO SB, single-breath diffusing capacity of the lung for carbon monoxide; ECG, electrocardiogram; EOS, end of study; FVC, forced vital capacity; HRCT, high-resolution computed tomography; IMP, Investigational Medicinal Product; PPF, progressive pulmonary fibrosis; L-PF, Living with Pulmonary Fibrosis Questionnaire; NRS, numeric rating scale; PBO, placebo; ppDLCO SB, percent predicted single-breath diffusing capacity of the lung for carbon monoxide; ppFVC, percent predicted forced vital capacity; QLF, quantitative lung fibrosis; SAE, serious adverse event.

^a EOS definition described herein.

^b Defined as an acute, clinically significant respiratory deterioration characterized by evidence of new, widespread alveolar abnormality.

Exploratory Objectives	Exploratory Endpoints
To evaluate the treatment effect of Compound A 60 and >60 mg BID, compared with PBO, on disease progression events from baseline through Week 52	- Proportion of participants with acute exacerbations of pulmonary fibrosis from baseline through Week 52 - Proportion of participants with respiratory-related hospitalizations from baseline through Week 52
To characterize the PK of Compound A in participants with PPF	Plasma concentrations of Compound A
To evaluate the effect of treatment on the rate of change in lung fibrosis as measured by HRCT through Week 104 and EOS^a	Change in QLF score via HRCT from baseline to Week 104, and baseline to EOS
To explore the trend of the patient-reported symptoms, impact of the disease, and overall health status over the duration of the study	Changes from baseline to EOS in EQ-5D-5L health utility index scores and visual analog scale scores
To assess the effect of Compound A on blood-based biomarkers	Change in blood-based biomarkers of lung fibrosis and inflammation from baseline to EOT
To assess the effects of lung fibrosis-related genes on drug response	Presence or absence of single nucleotide variants in genes associated with lung fibrosis from baseline to EOS
To assess the effect of genetic variations in genes associated with drug absorption, distribution, metabolism, excretion, and transport on the PK of Compound A	Presence or absence of single nucleotide polymorphism variants in genes encoding organic anion transporting polypeptides, CYP2C8, and breast cancer resistance protein from baseline to EOS

Abbreviations: BID, twice daily; CYP, cytochrome P450; EOS, end of study; HRCT, high-resolution computed tomography; PPF, progressive pulmonary fibrosis; PK, pharmacokinetic(s); QLF, quantitative lung fibrosis.

^a EOS definition described herein.

Treatment Period (Day 1 to End of Treatment)

[0287] The study ends when the last participant reaches Week 52. The treatment duration can be up to approximately 3.5 years for any one participant, depending on when a participant is enrolled.

Randomization

[0288] All participants will be randomized in a blinded manner as per the Interactive Response Technology (IRT) system. Two separate randomization sequences will be implemented for the 2 cohorts. Cohort 1 will randomize participants prior to Cohort 2. In Cohort 1, eligible participants will be randomized 1:1:1 to Compound A 60 mg, >60 mg and PBO, BID. The safety data from Cohort 1 will be reviewed at Week 4.

[0289] If the decision is to continue Compound A >60 mg in Cohort 1, Cohort 2 will enroll eligible participants and randomize 1:1:1 to Compound A 60 mg, >60 mg, and PBO, BID. If the decision is to discontinue Compound A >60 mg in Cohort 1, Cohort 2 will enroll eligible participants and randomize 1:1 to Compound 60 mg and PBO, BID.

Stratification

- [0290]** Randomization will be stratified by these factors for both Cohort 1 and Cohort 2:
- UIP Pattern (present vs absent) (UIP pattern to be verified during screening by centrally-read screening HRCT or previously obtained surgical lung biopsy or transbronchial cryobiopsy during previous clinical diagnostic evaluation of ILD). UIP pattern identification via cryobiopsy or by genomic classifier will be considered on a case-by-case basis (in collaboration with the Medical Monitor and central study team). UIP confirmation by genomic classifier will be considered on a case-by-case basis. This study will enroll approximately 60% of participants with verified UIP pattern at screening across all treatment arms.
 - Background therapy: anti-fibrotic therapy (pirfenidone or nintedanib with or without immunosuppression) vs. immunosuppression alone (mycophenolate mofetil [MMF], mycophenolic acid [MA], azathioprine [AZA], or tacrolimus) versus none.

Key Elements Day 1 to Week 52 include:

Primary endpoint at Week 52

- [0291]** No initiation or switching of anti-fibrotic therapies within the first 52 weeks
- [0292]** Visit 1 (Day 1/Week 1) includes randomization, first dose, spirometry, BP monitoring and other safety and clinical assessments.
- [0293]** Visits 2-4 (Week 1 to Week 2) are titration visits, 2-4 days apart, and includes dose escalation, BP monitoring, and overall safety assessments. Visits 2 and 3 can be on-site or tele-visits (eg, telephone, video, or virtual platform, as per site and country capability or regulation). See below for details of the BP titration phase.
- [0294]** Visits 5-13 (Week 4 through Week 52) are 6 weeks apart after Week 4 and include spirometry, routine BP monitoring and other safety and clinical assessments according to the Schedule of Assessments (contained in full protocol). Visits post-titration include the following week (W) visits: W4, W10, W16, W22, W28, W34, W40, W46, W52. See below for details of the Blood Pressure (BP) Monitoring Plan, which includes dose titration, BP assessments, and low BP criteria definitions.

Key Elements After Week 52 include:

- [0295] From Week 52 to end of study, visits occur every 12 weeks and include spirometry, routine BP monitoring and other safety and clinical assessments according to the Schedule of
- [0296] Assessments (contained in full protocol).
- [0297] Participants continue double-blind, placebo-controlled treatment for generating clinical efficacy and safety outcomes beyond Week 52.
- [0298] Study allows for potential escape to double-blind active treatment due to progressive disease based on the following Escape Criteria:
- [0299] Decline in absolute ppFVC of either:
≥10% within the previous 6 months, or
≥15% within the previous 12 months
and confirmed with a second visit at 4 to 12 weeks (with an unscheduled or next scheduled visit)
or
Respiratory-related respiratory hospitalization due to disease progression,
or
Acute Exacerbation
- [0300] If a participant meets eligibility for Escape Criteria, under blinded conditions the participant can escape to double-blind active treatment as follows:
Participants on PBO: randomized to 60 mg or higher BID dose
Participants on 60 mg: escalated to >60 mg BID dose
Participants on >60 mg: continue with >60 mg BID dose
- [0301] After Week 52, the initiation or switching of currently approved anti-fibrotic therapies (nintedanib or pirfenidone) are allowed, per PI discretion.
- [0302] Novel antifibrotic therapies that may become available after this study initiation are not allowed at any point during this study.
- [0303] All participants that have completed the study will have the option to participate in a separate Rollover Study with long-term active treatment.

Blood Pressure Monitoring Plan

BP Assessments:

[0304] Seated SBP measurements are assessed at pre-dose and post-dose at 1, 2, 4 hours according to the titration plan (see below). BP monitoring will be implemented in this study and actionable by the site if the following BP criteria are met at specific visit timepoints.

Low BP Criteria Definitions:

Low BP criteria for Visits 1, 2 and 3 (ie, initiation of 10, 30, 60 mg respectively):

- [0305] Seated SBP < 85 mmHg at 4 hours post-dose, or
- [0306] In the opinion of the investigator, there is a clinically significant, symptomatic event from a reduction in BP that warrants a pause in dose titration

Low BP criteria for Visit 4 (ie, initiation of >60 mg):

- [0307] Seated SBP < 85 mmHg at 4 hours post-dose, or
- [0308] Pre-dose to post-dose SBP decrease of $\geq 25\%$ and post-dose SBP is < 95 mmHg, or
- [0309] In the opinion of the investigator, there is a clinically significant, symptomatic event from a reduction in BP that warrants a pause in dose titration

4-step Dose Titration Phase (Day 1 – Day 10):*

[0310] The titration period is intended to be completed in 7 to 16 days with a minimum of 2 consecutive days of dosing required between titration visits. Overall, the titration period may be extended up to a maximum of 21 days to accommodate for unanticipated circumstances or logistics. If any low BP criteria are met during titration, refer to titration plan or discontinue treatment.

Table 28: Dose Titration Schedule for PBO vs. 60 mg vs >60 mg

Treatment Arm	*4-step Titration Scheme			
	Visit 1	**Visit 2	**Visit 3	Visit 4
PBO BID	PBO 10 mg	PBO 30 mg	PBO 60 mg	PBO >60 mg

60 mg BID	Compound A 10 mg	Compound A 30 mg	Compound A 60 mg	Compound A 60 mg
>60 mg BID	Compound A 10 mg	Compound A 30 mg	Compound A 60 mg	Compound A >60 mg

PBO = placebo.

** The titration period is intended to be 7 to 16 days. Each dose will be administered for approximately 2 to 3* days. The titration period may be extended up to a maximum of 21 days to accommodate unanticipated circumstances or logistics. All doses are taken PO BID throughout the study

Titration Plan:

- [0311] *Visit 1/Day 1 (Blinded 10 mg or PBO):* Participant receives blinded IMP (10 mg/PBO) for first time on Day 1.
- [0312] If post-dose low BP criteria are not met at 4 hours, continue with the next titration visit (Visit 2 to be completed in 2-3 days).
- [0313] If post-dose low BP criteria are met at 4 hours, hold evening dose, no further dosing and rechallenge with blinded 10 mg/PBO at next visit (**Visit 1A** to be completed within 14 days).
- [0314] If low BP criteria are not met at 4 hours post-dose with re-challenge, the participant continues with blinded 10 mg/PBO and proceeds with the next titration at **Visit 2**, to be completed in 2-3 days.
- [0315] If low BP criteria are met at 4 hours post-dose with re-challenge, the participant can be rechallenged again* at the PI discretion or treatment discontinued.
- [0316] *Visits 2 and 3 (V2: Blinded 30 mg or PBO; V3: Blinded 60 mg or PBO):*
Participant receives an increased blinded IMP (V2: 30 mg/PBO; V3: 60 mg/PBO) dose level for the first time. At the discretion of the site, investigator and/or participant, either an in-person visit, or a tele-visit will be conducted. For a tele-visit, home BP assessments will be performed via a standardized BP cuff provided by the sponsor vendor.)
- [0317] If post-dose low BP criteria are not met at 4 hours, continue with the next titration visit (Visit 3 or Visit 4 to be completed 2-3 days).
- [0318] If post-dose low BP criteria are met at 4 hours, the participant takes the previous blinded IMP (From V1: 10 mg/PBO for the evening of V2; From V2: 30 mg/PBO for evening of V3) for the evening dose, subsequent days and is rechallenged with blinded IMP (For V2A: 30 mg/PBO; For V3A: 60 mg/PBO) at next visit (**Visit 2A or 3A** to be completed within 7 days).

- [0319] If low BP criteria are not met at 4 hours post-dose with re-challenge, the participant continues with blinded IMP and proceeds with the next titration at **Visit 3 or Visit 4**, to be completed in 2-3 days.
- [0320] If low BP criteria are met at 4-hours post-dose with re-challenge, the participant can be rechallenged again* at the PI discretion or treatment discontinued.
- [0321] *Visit 4 (Blinded >60 mg or 60 mg or PBO)*: Some participants receive an increased blinded IMP at >60 mg for the first time, while others will continue to receive 60 mg or PBO.
- [0322] If post-dose low BP criteria are not met at 4 hours, continue with next visit schedule (**Visit 5** to be completed at Week 4).
- [0323] If post-dose low BP criteria are met at 4 hours, the participant takes previous blinded IMP (60 mg/PBO) for the evening dose, subsequent days and is rechallenged with blinded IMP (>60 mg/60 mg/PBO) at next visit (**Visit 4A** to be completed within 7 days).
- [0324] If low BP criteria are not met at 4 hours post-dose with re-challenge, the participant continues with blinded 60 mg/PBO and proceeds to Week 4 with **Visit 5**, to be completed in 2-3 days.
- [0325] If low BP criteria are met at 4-hours post-dose with re-challenge, the participant can be rechallenged again* at the PI discretion or treatment discontinued.
- [0326] *Over the course of titration plan, if the participant would need to be re-challenged more than twice, the sponsor's medical monitor or study director must be consulted.
- [0327] *For each titration visit, participants are encouraged to have a snack or small meal prior to dosing.

Table 29: Visit Schedule for Dose Titration and Actionable Rules

Low BP Criteria	Visit 1 Initiation 10 mg ^a	Visit 2 Initiation 30 mg ^a	Visit 3 Initiation of 60 mg ^a	Visit 4 Initiation of >60 mg ^a or continuation of 60 mg ^a
Not Met	Initiate 10 mg and proceed to Visit 2.	Continue 30 mg and proceed to Visit 3.	Continue 60 mg and proceed to Visit 4.	Continue >60 or 60 mg and proceed to Visit 5.
Met	Hold further dosing and rechallenge with 10 mg at next visit. ^b	Return to the prior dose (10 mg) and rechallenge with	Return to the prior dose (30 mg) and rechallenge with	Return to the prior dose (60 mg) and rechallenge with

Low BP Criteria	Visit 1	Visit 2	Visit 3	Visit 4
	Initiation 10 mg ^a	Initiation 30 mg ^a	Initiation of 60 mg ^a	Initiation of >60 mg ^a or continuation of 60 mg ^a
		30 mg at next visit. ^b	60 mg at next visit. ^b	>60 mg at next visit. ^b

Abbreviations: BP, blood pressure; PBO, placebo.

^a Compound A or PBO dose.

^b Rechallenge at the next visit and refer to above if any low BP criteria are met at a titration step visit. Participants may be rechallenged 2 times within or across dose levels. If any low BP criteria are met a third time, the participant should be treatment discontinued, or the site must consult the Medical Monitor for another potential rechallenge. For each titration visit, participants are encouraged to have a snack or a small meal prior to dosing.

EXAMPLE 6: A Multicenter, Randomized, Double-blind, Placebo-controlled, Phase 3 study to evaluate the Efficacy, Safety, and Tolerability of Compound A in Participants with Idiopathic Pulmonary Fibrosis (IPF).

Scientific Rationale for Study Design

Rationale for the Titration Phase:

[0328] Reductions in BP were noted with first dose administration of Compound A at 30 or 60 mg BID in the Phase 2 study and at the same as well as higher doses in Phase 1 studies. PK/PD modeling and simulation suggests that Day 1 post-dose reductions in BP observed in the study may be mitigated by dose titration. Therefore, a dose titration plan is being implemented with BP monitoring for safety and to evaluate the impact of dose titration on BP and clinical events related to low BP.

Rationale for the Study Design:

[0329] The primary endpoint of Cohort 1 is the number of spontaneous syncopal episodes that occur in the Compound A >60 mg and PBO arms after the first dose of Compound A >60 mg until the Week 4 visit. In the Phase 2 study, no syncope events occurred in the Compound A 30 and 60 mg arms. Post-dose reductions in SBP were observed in these arms on Day 1 of dosing and these reductions were self-limited and not associated with any clinical sequelae. Spontaneous syncope is a clinically meaningful indicator of hypotension and will be monitored and reviewed in Cohort 1 of the study to enable the decision to proceed with the Compound A >60 mg dose.

[0330] The primary endpoint chosen for Cohort 2 this Phase 3 study, specifically absolute decline in FVC (mL), is similar to that in other IPF trials for approved therapies. The Phase 3 pirfenidone and nintedanib IPF trials demonstrated benefits on FVC in patients receiving active treatment, compared with PBO, after 72 weeks and 52 weeks of treatment, respectively. Furthermore, a 10% or greater absolute reduction in FVC over a 6-month period has been shown to be associated with an almost five-fold increase in the risk of death over the subsequent 1-year period. A decline in FVC of only 10% was also predictive, with a greater than two-fold increased risk of death over the subsequent year. Collectively, it has been established that FVC represents a robust clinical measurement that is a standard for the determination of progression of disease whereby categorical decrements of FVC are powerful predictors of mortality.

[0331] The secondary endpoints chosen for Cohort 2 in this Phase 3 study are similar to those in other IPF trials and well suited to reliably assess efficacy and safety. This Phase 3 study will extend the placebo-controlled period beyond 52 weeks to increase the likelihood of demonstrating that Compound A demonstrates clinically meaningful benefits beyond FVC, for example, respiratory-related respiratory hospitalization, acute exacerbations, patient-reported outcome (PRO) data, and potentially even survival, adverse events (AEs), significant adverse events (SAEs), and other safety assessments.

[0332] Given the extension of the placebo-controlled period beyond 52 weeks, and that this participant population may require emergency care, disease worsening criteria have been incorporated into the study, participants that have disproportionate declines in FVC over time or who experience acute exacerbations or hospitalization related to lung fibrosis progression will be able to transition to double-blind active investigational therapy.

STUDY POPULATION

Key Inclusion Criteria

[0333] Participants are eligible to be included in the study if all the following criteria apply:

- 1) ≥ 40 years of age at the time of signing the informed consent form (ICF).
- 2) Diagnosis of IPF within 7 years prior to screening.
- 3) Diagnosis of IPF is supported by centrally read chest high-resolution computed tomography (HRCT) obtained at screening:

- HRCT interpretation is consistent with definite UIP or probable UIP.
 - If the HRCT interpretation on central reading is inconsistent with UIP (indeterminate or most consistent with non-IPF diagnosis), there must be verification that surgical lung biopsy histopathology is consistent with UIP. UIP pattern identification via cryobiopsy or by genomic classifier will be considered on a case-by-case basis (in collaboration with the Medical Monitor and central study team).
- 4) Percent Predicted Forced Vital Capacity (ppFVC) ≥ 40 %.
 - 5) Forced expiratory volume in 1 second (FEV1)/FVC ≥ 0.7 .
 - 6) Single-breath, hemoglobin-corrected, percent predicted diffusion capacity of the lung for carbon monoxide (DLCO) $\geq 25\%$.
 - 7) If on pirfenidone or nintedanib, participants must have been receiving a stable dose for at least 90 days prior to screening.
 - 8) If not currently on pirfenidone or nintedanib, participants must not have received either of these medications within 28 days prior to screening.
 - 9) Women who are of childbearing potential must have a highly effective form of contraception (if hormonal method is used, a barrier method must also be used).
 - Negative pregnancy serum test prior to Day 1 and negative pregnancy urine/serum test on Day 1, prior to study treatment administration.
 - 10) Men who are sexually active with WOCBP agree to use male barrier contraception.

[0334] A study with IPF will be randomized to receive Compound A at 60 mg or higher or matching placebo orally twice daily (BID) at a ratio of 1:1:1. Approximately equal number of participants will be randomized to each treatment arm. Stable, background standard of care (SOC) therapy for IPF with nintedanib or pirfenidone will be allowed. Similarly, select background immunosuppressive therapies targeting ILD will be allowed. The study will utilize a 2-cohort design:

[0335] Cohort 1 is a single-blind design. The study team, investigators, participants and families are blinded to participant-level treatment assignments, whereas an internal review committee (IRC) will be unblinded to all Cohort 1 data. Cohort 1 will enroll approximately 60 participants with IPF to evaluate the safety and tolerability of Compound A. Eligible participants will be randomized 1:1:1 to Compound A 60 mg or

>60 mg, or PBO, BID. Cohort 1 will enroll and randomize participants prior to Cohort 2. Cohort 2 will subsequently enroll and randomize participants with IPF based on evaluation of spontaneous syncopal events (defined as a clinical syndrome in which transient loss of consciousness is caused by a period of inadequate cerebral blood flow and oxygenation, most often the result of an abrupt drop of systemic BP, associated with spontaneous recovery in a participant without medical history of syncope) from Cohort 1. Spontaneous syncopal episodes will be evaluated in the Compound A > 60 mg treatment arm as compared with PBO to determine one of the following decisions:

- To continue Cohort 1 without modification (fewer than 2 spontaneous syncopal episodes without plausible alternative etiology in the Compound A > 60 mg arm compared with PBO, and without an undesirable safety profile compared with PBO; assessment will be performed by the IRC) and initiate with Compound A 60 mg, > 60 mg, and PBO arms in Cohort 2

OR

- To terminate the Compound A >60 mg arm in Cohort 1 (2 or more spontaneous syncopal episodes without plausible alternative etiology in the Compound A >60 mg arm compared with PBO, or with an undesirable safety profile compared with PBO; assessment will be performed by the IRC). All participants in the Compound >60 mg arm in Cohort 1 will complete an early termination visit, and will be encouraged to complete a safety follow-up visit approximately 28 days after the last dose of IMP. Participants in Cohort 1 in the blinded Compound A 60 mg or PBO arms will continue in Cohort 1 through EOS. If the IRC determines that the Compound A >60 mg arm is discontinued in Cohort 1, then this dose will not be initiated in Cohort 2, and Cohort 2 will only include the Compound A 60 mg and PBO arms.

[0336] Cohort 2 is a registrational, double-blind design, whereby Sponsor, investigators, participants and families will remain blinded to treatment assignments. Cohort 2 will investigate the efficacy, safety, and tolerability of Compound A compared with PBO. Treatment arms in Cohort 2 will be determined by the outcome of the IRC review of Cohort 1 data and will result in one of the following options:

- Three treatment arms: Approximately 1125 participants with IPF will be randomized 1:1:1 to Compound A 60 mg or >60 mg, or PBO, BID.

OR

- Two treatment arms: Approximately 750 participants with IPF will be randomized 1:1 Compound A 60 mg or PBO, BID.

Screening period (Up to 6 weeks)

[0337] *Treatment period* is approximately 4 years from the Day 1 visit for the first randomized participant in Cohort 1 through the last participant's end of treatment (EOT) visit in Cohort 2 (a participant's individual study duration could be from a minimum of 52 weeks up to approximately 4 years depending on when last participant completes the Week 52 visit endpoint):

[0338] Titration period: Day 1 (day of first dose of IMP) up to Day 16 with a minimum of 2 consecutive days of dosing required between titration visits. If any low BP criteria are met during titration, participants must either be rechallenged at the next visit or discontinue treatment.

Post-titration period until EOT.

[0339] EOT is defined as when each participant completes their last scheduled treatment visit as per the Schedule of Activities. The EOT visit for the last participant is defined as completion of Week 52 visit. The EOT visit is triggered for all participants on treatment when the date of the projected Week 52 visit is known for the last participant.

[0340] The primary endpoint is captured at Week 52.

[0341] The last participant is defined as the participant to complete the safety follow-up visit last.

[0342] Visit and enters the Rollover Study or has the Safety Follow-up visit.

[0343] *Post-treatment safety follow-up (SFU) period* (28 days following the last dose of IMP).

OBJECTIVES AND ENDPOINTS

[0344] The primary objective of Cohort 1 is to assess the safety of the Compound A >60 mg BID dose through the Week 4 visit. The primary endpoint of Cohort 1 is the number of spontaneous syncopal episodes that occur in the Compound A and PBO arms during the period that starts with the first dose of Compound A and ends with the Week 4 visit.

[0345] The secondary objective of Cohort 1 is to assess the safety and tolerability of Compound A 60 and >60 mg BID, compared with PBO, through end of study. The secondary endpoints include the discontinuation rate due to any AE related to low BP and safety assessments of Compound A 60 mg and >60 mg compared with PBO through EOS.

[0346] Cohort 2 primary, key secondary, secondary, and exploratory objectives are shown below:

Primary Objectives and Endpoints for Cohort 2

Objectives	Endpoints
Primary To evaluate the efficacy of two doses of Compound A, 60 mg and a dose higher than 60 mg twice daily (BID), compared to matching placebo (PBO), demonstrating improvement in absolute change in FVC from baseline at Week 52.	Primary Absolute change in FVC (mL) from baseline at Week 52

Key Secondary Objectives and Endpoints

Objectives	Endpoints
Key Secondary - To evaluate the effect of Compound A 60 and a >60 mg dose BID, compared with PBO, on disease progression from baseline through EOS^a - To evaluate the effect of Compound A 60 mg and >60 mg BID, compared with PBO on quality of life and morbidity from baseline to Week 52.	Key Secondary ⌋ Disease progression 4-component composite endpoint: Time to first disease progression event in at least one of the following, from Day 1 to EOS: – Absolute ppFVC decline of $\geq 10\%$ from baseline – Acute exacerbation of pulmonary fibrosis – Respiratory-related hospitalization – All-cause mortality ⌋ Change in L-PF cough domain score from baseline to Week 52. ⌋ Change in L-PF dyspnea score from baseline to Week 52. ⌋ Change in walking distance measured in 6MWT from baseline at Week 52

Secondary Objectives and Endpoints

Objectives	Endpoints
To evaluate the treatment effect of 2 doses of Compound A, 60 and > 60 mg BID, compared with PBO, on	Time to first occurrence of at least 1 of the following events, from baseline up to EOS:

– Selected clinical assessments from baseline to Week 52 – Disease progression events from baseline up to EOS^a	– Acute exacerbation of pulmonary fibrosis^b – Respiratory-related hospitalization – All-cause mortality • Time to absolute ppFVC decline of $\geq 10\%$ from Day 1 through EOS • Time to first acute exacerbation of pulmonary fibrosis from Day 1 through EOS • Time to first lung fibrosis-related hospitalization from Day 1 through EOS • Time to all-cause mortality from Day 1 through EOS • Changes in remaining L-PF fatigue domain and impact module scores from baseline at Week 52 • Changes in Cough NRS from baseline at Week 52 • Changes in EQ-5D-5L health utility index scores and visual analog scale scores from baseline at Week 52 • Rate of decline in FVC (mL) from baseline at Week 52 • Rate of decline in ppFVC (%) from baseline at Week 52 • Change in ppFVC from baseline at Week 52 • Proportion of participants with absolute decline in ppFVC $\geq 10\%$ at Week 52 • Proportion of participants with relative decline in ppFVC $\geq 10\%$ at Week 52 • Change in L-PF cough domain score from baseline at Week 52 (secondary endpoint in EU only) • Change in L-PF dyspnea domain score from baseline at Week 52 (secondary endpoint in EU only) • Change in DLCO SB (mL/min/mm Hg) (corrected for hemoglobin) from baseline at Week 52
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Objectives	Endpoints
	• Change in ppDLCO SB (%) (corrected for hemoglobin) from baseline at Week 52 • Change in QLF score via HRCT from baseline at Week 52
• To explore the trend of the patient-reported symptoms, impact of the disease and overall health status over the duration of the study	• Changes from baseline to EOS in – Patient-reported symptoms and impacts of the disease as assessed by the L-PF cough, dyspnea, and fatigue domain scores, and impacts module scores – Cough NRS
• To evaluate the safety and tolerability of Compound A in participants randomized to receive Compound A at 60 or >60 mg BID, compared with PBO, through Week 52 and up to EOS	• AEs • SAEs • AEs leading to early discontinuation of IMP • Treatment-emergent deaths • Clinical laboratory findings • ECGs • Vital signs

Abbreviations: AE, adverse event; BID, twice daily; DLCO SB, single-breath diffusing capacity of the lung for carbon monoxide; ECG, electrocardiogram; EOS, end of study; FVC, forced vital capacity; HRCT, high-resolution computed tomography; IMP, Investigational Medicinal Product; IPF, idiopathic pulmonary fibrosis; L-PF, Living with Pulmonary Fibrosis Questionnaire; NRS, numeric rating scale; PBO, placebo; ppDLCO SB, percent predicted single-breath diffusing capacity of the lung for carbon monoxide; ppFVC, percent predicted forced vital capacity; QLF, quantitative lung fibrosis; SAE, serious adverse event.

^a EOS definition described herein.

^b Defined as an acute, clinically significant respiratory deterioration characterized by evidence of new, widespread alveolar abnormality.

Exploratory Objectives and Endpoints

Objectives	Endpoints
• To evaluate the treatment effect of Compound A 60 and >60 mg BID, compared with PBO, on disease progression events from baseline through Week 52	• Proportion of participants with acute exacerbations of pulmonary fibrosis from baseline through Week 52 • Proportion of participants with respiratory-related hospitalizations from baseline through Week 52
• To characterize the PK of Compound A	• Plasma concentrations of Compound A
• To evaluate the effect of treatment on the rate of change in lung fibrosis as measured by HRCT through Week 104 and EOS	• Change in QLF score via HRCT from baseline to Week 104, and baseline to EOS

Objectives	Endpoints
To explore the trend of the patient-reported symptoms, impact of the disease, and overall health status over the duration of the study	Changes from baseline to EOS in EQ-5D-5L health utility index scores and visual analog scale scores
To assess the effect of Compound A on blood-based biomarkers	Change in blood-based biomarkers of lung fibrosis and inflammation from baseline to EOT
To assess the effects of IPF-related genes on drug response	Presence or absence of single nucleotide variants in genes associated with lung fibrosis from baseline to EOS
To assess the effect of genetic variations in genes associated with drug absorption, distribution, metabolism, excretion, and transport on the PK of Compound A	Presence or absence of single nucleotide polymorphism variants in genes encoding organic anion transporting polypeptides, CYP2C8, and breast cancer resistance protein from baseline to EOS

Abbreviations: BID, twice daily; CYP, cytochrome P450; EOS, end of study; HRCT, high-resolution computed tomography; IPF, idiopathic pulmonary fibrosis; PK, pharmacokinetic(s); QLF, quantitative lung fibrosis.

Treatment Period (Day 1 to End of Treatment)

[0347] The study ends when the last participant reaches Week 52. The treatment duration can be up to approximately 3.5 years for any one participant, depending on when a participant is enrolled.

Randomization

[0348] All participants will be randomized in a blinded manner as per the Interactive Response Technology (IRT) system. Two separate randomization sequences will be implemented for the 2 cohorts. Cohort 1 will randomize participants prior to Cohort 2. In Cohort 1, eligible participants will be randomized 1:1:1 to Compound A 60 mg, >60 mg and PBO, BID. The safety data from Cohort 1 will be reviewed at Week 4.

[0349] If the decision is to continue Compound A >60 mg in Cohort 1, Cohort 2 will enroll eligible participants and randomize 1:1:1 to Compound A 60 mg, >60 mg, and PBO, BID. If the decision is to discontinue Compound A >60 mg in Cohort 1, Cohort 2 will enroll eligible participants and randomize 1:1 to Compound A 60 mg and PBO, BID.

Stratification

[0350] Randomization will be stratified by these factors for both Cohort 1 and Cohort 2:

- Concomitant use of approved IPF therapy (pirfenidone versus nintedanib versus none)
- Sex (male versus female)

Key Elements Day 1 to Week 52 include:

Primary endpoint at Week 52

- [0351] No initiation or switching of anti-fibrotic therapies within the first 52 weeks
- [0352] Visit 1 (Day 1/Week 1) includes randomization, first dose, spirometry, BP monitoring and other safety and clinical assessments.
- [0353] Visits 2-4 (Week 1 to Week 2) are titration visits, 2-4 days apart, and includes dose escalation, BP monitoring, and overall safety assessments. Visits 2 and 3 can be on-site or tele-visits (eg, telephone, video, or virtual platform, as per site and country capability or regulation). See below for details of the BP titration phase.
- [0354] Visits 5-13 (Week 4 through Week 52) are 6 weeks apart after Week 4 and include spirometry, routine BP monitoring and other safety and clinical assessments according to the Schedule of Assessments (contained in full protocol). Visits post-titration include the following week (W) visits: W4, W10, W16, W22, W28, W34, W40, W46, W52.
- [0355] See below for details of the Blood Pressure (BP) Monitoring Plan, which includes dose titration, BP assessments, and low BP criteria definitions.

Key Elements After Week 52 include:

- [0356] From Week 52 to end of study, visits occur every 12 weeks and include spirometry, routine BP monitoring and other safety and clinical assessments according to the Schedule of Assessments (contained in full protocol).
- [0357] Participants continue double-blind, placebo-controlled treatment for generating clinical efficacy and safety outcomes beyond Week 52.
- [0358] Study allows for potential escape to double-blind active IMP treatment due to progressive disease based on the following Escape Criteria:
- [0359] Decline in absolute ppFVC of either:
 $\geq 10\%$ within the previous 6 months, or
 $\geq 15\%$ within the previous 12 months and confirmed with a second visit at 4 to 12 weeks (with an unscheduled or next scheduled visit)
or
IPF-related respiratory hospitalization due to disease progression,
or

Acute Exacerbation

- [0360] If a participant meets eligibility for Escape Criteria, under blinded conditions the participant can escape to double-blind active treatment as follows:
- Participants on PBO: randomized to 60 mg or higher BID dose
- Participants on 60 mg: escalated to >60 mg BID dose
- Participants on >60 mg: continue with >60 mg BID dose
- [0361] After Week 52, the initiation or switching of currently approved anti-fibrotic therapies (nintedanib or pirfenidone) are allowed, per PI discretion.
- [0362] Novel antifibrotic therapies that may become available after this study initiation are not allowed at any point during this study.
- [0363] All participants that have completed the study will have the option to participate in a separate Rollover Study with long-term active treatment.

*Blood Pressure Monitoring Plan**BP Assessments:*

- [0364] Seated SBP measurements are assessed at pre-dose and post-dose at 1, 2, 4 hours according to the titration plan (see below). BP monitoring will be implemented in this study and actionable by the site if the following BP criteria are met at specific visit timepoints.

*Low BP Criteria Definitions:**Low BP criteria for Visits 1, 2 and 3 (ie, initiation of 10, 30, 60 mg respectively):*

- [0365] Seated SBP < 85 mmHg at 4 hours post-dose, or
- [0366] In the opinion of the investigator, there is a clinically significant, symptomatic event from a reduction in BP that warrants a pause in dose titration

Low BP criteria for Visit 4 (ie, initiation of >60 mg):

- [0367] Seated SBP < 85 mmHg at 4 hours post-dose, or
- [0368] Pre-dose to post-dose SBP decrease of $\geq 25\%$ and post-dose SBP is < 95 mmHg,
or
- [0369] In the opinion of the investigator, there is a clinically significant, symptomatic event from a reduction in BP that warrants a pause in dose titration

4-step Dose Titration Phase (Day 1 – Day 10):*

- [0370]** The titration period is intended to be completed in 7 to 16 days with a minimum of 2 consecutive days of dosing required between titration visits. Overall, the titration period may be extended up to a maximum of 21 days to accommodate for unanticipated circumstances or logistics. If any low BP criteria are met during titration, refer to titration plan or discontinue treatment.

Table 30: Dose Titration Schedule for PBO vs. 60 mg vs >60 mg

Treatment Arm	*4-step Titration Scheme			
	Visit 1	Visit 2	Visit 3	Visit 4
PBO BID	PBO 10 mg	PBO 30 mg	PBO 60 mg	PBO >60 mg
60 mg BID	Compound A 10 mg	Compound A 30 mg	Compound A 60 mg	Compound A 60 mg
>60 mg BID	Compound A 10 mg	Compound A 30 mg	Compound A 60 mg	Compound A >60 mg

PBO = placebo.

** The titration period is intended to be 7 to 16 days. Each dose will be administered for approximately 2 to 3 days. The titration period may be extended up to a maximum of 21 days to accommodate unanticipated circumstances or logistics. All doses are taken PO BID throughout the study.

Titration Plan:

- [0371]** *Visit 1/Day 1 (Blinded 10 mg or PBO):* Participant receives blinded IMP (10 mg/PBO) for first time on Day 1.
- [0372]** If post-dose low BP criteria are not met at 4 hours, continue with the next titration visit (Visit 2 to be completed in 2-3 days).
- [0373]** If post-dose low BP criteria are met at 4 hours, hold evening dose, no further dosing and rechallenge with blinded 10 mg/PBO at next visit (Visit 1A to be completed within 14 days).
- [0374]** If low BP criteria are not met at 4 hours post-dose with re-challenge, the participant continues with blinded 10 mg/PBO and proceeds with the next titration at Visit 2, to be completed in 2-3 days.
- [0375]** If low BP criteria are met at 4 hours post-dose with re-challenge, the participant can be rechallenged again* at the PI discretion or treatment discontinued.

- [0376]** *Visits 2 and 3 (V2: Blinded 30 mg or PBO; V3: Blinded 60 mg or PBO):*
Participant receives an increased blinded IMP (V2: 30 mg/PBO; V3: 60 mg/PBO) dose level for the first time. At the discretion of the site, investigator and/or participant, either an in-person visit, or a tele-visit will be conducted. For a tele-visit, home BP assessments will be performed via a standardized BP cuff provided by the sponsor vendor.)
- [0377]** If post-dose low BP criteria are not met at 4 hours, continue with the next titration visit (Visit 3 or Visit 4 to be completed 2-3 days).
- [0378]** If post-dose low BP criteria are met at 4 hours, the participant takes the previous blinded IMP (From V1: 10 mg/PBO for the evening of V2; From V2: 30 mg/PBO for evening of V3) for the evening dose, subsequent days and is rechallenged with blinded IMP (For V2A: 30 mg/PBO; For V3A: 60 mg/PBO) at next visit (Visit 2A or 3A to be completed within 7 days).
- [0379]** If low BP criteria are not met at 4 hours post-dose with re-challenge, the participant continues with blinded IMP and proceeds with the next titration at Visit 3 or Visit 4, to be completed in 2-3 days.
- [0380]** If low BP criteria are met at 4-hours post-dose with re-challenge, the participant can be rechallenged again* at the PI discretion or treatment discontinued.
- [0381]** *Visit 4 (Blinded >60 mg or 60 mg or PBO):* Some participants receive an increased blinded IMP at >60 mg for the first time, while others will continue to receive 60 mg or PBO.
- [0382]** If post-dose low BP criteria are not met at 4 hours, continue with next visit schedule (Visit 5 to be completed at Week 4).
- [0383]** If post-dose low BP criteria are met at 4 hours, the participant takes previous blinded IMP (60 mg/PBO) for the evening dose, subsequent days and is rechallenged with blinded IMP (>60 mg/60 mg/PBO) at next visit (Visit 4A to be completed within 7 days).
- [0384]** If low BP criteria are not met at 4 hours post-dose with re-challenge, the participant continues with blinded 60 mg/PBO and proceeds to Week 4 with Visit 5, to be completed in 2-3 days.
- [0385]** If low BP criteria are met at 4-hours post-dose with re-challenge, the participant can be rechallenged again* at the PI discretion or treatment discontinued.

- [0386] *Over the course of titration plan, if the participant would need to be re-challenged more than twice, the sponsor’s medical monitor or study director must be consulted.
- [0387] *For each titration visit, participants are encouraged to have a snack or small meal prior to dosing.

Table 31: Visit Schedule for Dose Titration and Actionable Rules

Low BP Criteria	Visit 1 Initiation 10 mg ^a	Visit 2 Initiation 30 mg ^a	Visit 3 Initiation of 60 mg ^a	Visit 4 Initiation of >60 mg ^a or continuation of 60 mg ^a
Not Met	Initiate 10 mg and proceed to Visit 2.	Continue 30 mg and proceed to Visit 3.	Continue 60 mg and proceed to Visit 4.	Continue >60 or 60 mg and proceed to Visit 5.
Met	Hold further dosing and rechallenge with 10 mg at next visit. ^b	Return to the prior dose (10 mg) and rechallenge with 30 mg at next visit. ^b	Return to the prior dose (30 mg) and rechallenge with 60 mg at next visit. ^b	Return to the prior dose (60 mg) and rechallenge with >60 mg at next visit. ^b

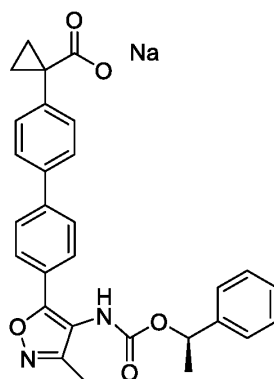
Abbreviations: BP, blood pressure; PBO, placebo.

^a Compound A or PBO dose.

^b Rechallenge at the next visit and refer to above if any low BP criteria are met at a titration step visit. Participants may be rechallenged 2 times within or across dose levels. If any low BP criteria are met a third time, the participant should be treatment discontinued, or the site must consult the Medical Monitor for another potential rechallenge. For each titration visit, participants are encouraged to have a snack or a small meal prior to dosing.

EXAMPLE 7: Effect of Single Dose of Compound B on Blood Pressure

- [0388] The compound sodium (R)-1-(4'-(3-methyl-4-(((1-phenylethoxy)carbonyl)amino)isoxazol-5-yl)-[1,1'-biphenyl]-4-yl)cyclopropane-1-carboxylate (hereafter referred as to “Compound B”) is an LPA1 antagonist having the structure shown below:



Compound B

and is described in U.S. Patent Application Publication No. 2010/0311799. Single ascending dose of Compound B caused a drop in blood pressure starting ~1.25 hr post dose (Fig. 5). After multiple days of dosing shows the same effect but further shows normalization of blood pressure by approximately day 3 (Fig. 6).

[0389] It is to be appreciated that the Detailed Description section, and not the Summary and Abstract sections, is intended to be used to interpret the claims. The Summary and Abstract sections may set forth one or more but not all exemplary aspects of the present disclosure as contemplated by the inventor(s), and thus, are not intended to limit the present disclosure and the appended claims in any way.

[0390] The present disclosure has been described above with the aid of functional building blocks illustrating the implementation of specified functions and relationships thereof. The boundaries of these functional building blocks have been arbitrarily defined herein for the convenience of the description. Alternate boundaries can be defined so long as the specified functions and relationships thereof are appropriately performed.

[0391] The foregoing description of the specific aspects will so fully reveal the general nature of the disclosure that others can, by applying knowledge within the skill of the art, readily modify and/or adapt for various applications such specific aspects, without undue experimentation, without departing from the general concept of the present disclosure. Therefore, such adaptations and modifications are intended to be within the meaning and range of equivalents of the disclosed aspects, based on the teaching and guidance presented herein. It is to be understood that the phraseology or terminology herein is for the purpose of description and not of limitation, such that the terminology or phraseology

of the present specification is to be interpreted by the skilled artisan in light of the teachings and guidance.

[0392] The breadth and scope of the present disclosure should not be limited by any of the above-described exemplary aspects, but should be defined only in accordance with the following claims and their equivalents.

WHAT IS CLAIMED IS:

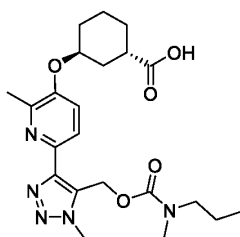
1. A method of treating interstitial lung disease in a subject in need thereof, the method comprising administering an LPA₁ antagonist to the subject at one or more daily dosages lower than the standard daily dosage during a dose titration period of treatment then increasing the daily dosage to the standard daily dosage of the LPA₁ antagonist.
2. The method of claim 1, wherein the dose titration period of treatment is completed within 21 days.
3. The method of claim 1 or 2, wherein the dose titration period of treatment is completed within 14 days.
4. The method of any one of claims 1 to 3, wherein the dose titration period of treatment is completed within 10 days.
5. The method of any one of claims 1 to 4, wherein the dose titration period of treatment is completed within 7 days.
6. The method of any one of claims 1 to 5, wherein the dose titration period of treatment is completed within 5 days.
7. The method of any one of claims 1 to 6, wherein the dose titration period of treatment comprises an initial period of treatment and a second period of treatment.
8. The method of claim 7, wherein the initial period of treatment is completed within 7 days.
9. The method of claim 7 or 8, wherein the initial period of treatment is completed within 4 days.
10. The method of any one of claims 7 to 9, wherein the initial period of treatment is completed within 3 days.

11. The method of any one of claims 7 to 10, wherein the initial period of treatment is completed within 2 days.
12. The method of any one of claims 7 to 11, wherein the initial period of treatment is completed within 1 day.
13. The method of any one of claims 7 to 12, wherein the second period of treatment is completed within 7 days.
14. The method of any one of claims 7 to 13, wherein the second period of treatment is completed within 4 days.
15. The method of any one of claims 7 to 14, wherein the second period of treatment is completed within 3 days.
16. The method of any one of claims 7 to 15, wherein the second period of treatment is completed within 2 days.
17. The method of any one of claims 7 to 16, wherein the second period of treatment is completed within 1 day.
18. The method of any one of claims 7 to 17, wherein the dose titration period of treatment further comprises a third period of treatment.
19. The method of claim 18, wherein the third period of treatment is completed within 7 days.
20. The method of claim 18 or 19, wherein the third period of treatment is completed within 4 days.
21. The method of any one of claims 18 to 20, wherein the third period of treatment is completed within 3 days.
22. The method of any one of claims 18 to 21, wherein the third period of treatment is completed within 2 days.

23. The method of any one of claims 18 to 22, wherein the third period of treatment is completed within 1 day.
24. A method of treating interstitial lung disease in a subject in need thereof, the method comprising administering an LPA₁ antagonist to the subject at a daily dosage lower than the standard daily dosage during an initial period of treatment, followed by administering the dosage at a daily dosage higher than the initial period but lower than the standard daily dosage for a second period of treatment, then increasing the dosage to the standard daily dosage of the LPA₁ antagonist.
25. The method of claim 24, wherein the initial period of treatment and the second period of treatment are each independently completed within 7 days.
26. The method of claim 24 or 25, wherein the initial period of treatment and the second period of treatment are each independently completed within 4 days.
27. The method of any of claims 24 to 26, wherein the initial period of treatment and the second period of treatment are each independently completed within 3 days.
28. The method of any of claims 24 to 27, wherein the initial period of treatment and the second period of treatment are each independently completed within 2 days.
29. The method of any of claims 24 to 28, wherein the initial period of treatment and the second period of treatment are each independently completed within 1 day.
30. The method of claim 24, wherein increasing the dosage comprises administering the dosage at a daily dosage lower than the standard daily dosage for a third period of treatment, then administering the standard daily dosage for a fourth period of treatment.
31. The method of claim 30, wherein the third period of treatment is completed within 7 days.
32. The method of claim 30 or 31, wherein the third period of treatment is completed within 4 days.

33. The method of any of claims 30 to 32, wherein the third period of treatment is completed within 3 days.
34. The method of any of claims 30 to 33, wherein the third period of treatment is completed within 2 days.
35. The method of any of claims 30 to 34, wherein the third period of treatment is completed within 1 day.
36. The method of any one of claims 1 to 35, wherein the LPA₁ antagonist is administered once a day.
37. The method of any one of claims 1 to 36, wherein the LPA₁ antagonist is administered twice a day.
38. The method of any one of claims 1 to 37, wherein the LPA₁ antagonist is administered orally.
39. The method of any one of claims 1 to 38, wherein the LPA₁ antagonist is administered as a tablet.
40. The method of any one of claims 1 to 39, wherein the subject is being treated with one or more additional therapies for interstitial lung disease.
41. The method claim 40 wherein the one or more additional therapies is pirfenidone.
42. The method of claim 40, wherein the one or more additional therapies is ninedanib.
43. The method of any one of claims 1 to 42, wherein the LPA₁ antagonist is administered with food.
44. The method of any one of claims 1 to 43, wherein the LPA₁ antagonist is administered without food.

45. The method of any one of claims 1 to 44, wherein the interstitial lung disease is idiopathic pulmonary fibrosis (IPF).
46. The method of any one of claims 1 to 44, wherein the interstitial lung disease is progressive pulmonary fibrosis (PPF).
47. The method of any one of claims 1 to 46, wherein the LPA₁ antagonist is Compound A:



Compound A;

- or a pharmaceutically acceptable salt thereof, and the standard daily dosage is about 120 mg/day of Compound A or an equivalent amount of a pharmaceutically acceptable salt thereof.
48. The method of claim 47, wherein the standard daily dosage of Compound A is about 60 mg twice daily or an equivalent amount of a pharmaceutically acceptable salt thereof.
49. The method of any one of claims 7 to 48, wherein the LPA₁ antagonist is Compound A, or a pharmaceutically acceptable salt thereof, and wherein about 20 mg/day of Compound A, or an equivalent amount of a pharmaceutically acceptable salt thereof, is administered during the initial period of treatment.
50. The method of any one of claims 7 to 49, wherein the LPA₁ antagonist is Compound A, or a pharmaceutically acceptable salt thereof, and wherein about 10 mg twice daily of Compound A, or an equivalent amount of a pharmaceutically acceptable salt thereof, is administered during the initial period of treatment.
51. The method of any one of claims 7 to 50, wherein the LPA₁ antagonist is Compound A, or a pharmaceutically acceptable salt thereof, and wherein about 60 mg/day of Compound

A, or an equivalent amount of a pharmaceutically acceptable salt thereof, is administered during the second treatment period.

52. The method of any one of claims 7 to 51 wherein the LPA₁ antagonist is Compound A, or a pharmaceutically acceptable salt thereof, and wherein about 30 mg twice daily of Compound A, or an equivalent amount of a pharmaceutically acceptable salt thereof, is administered during the second treatment period.

53. The method of any one of claims 47 to 52, wherein Compound A comprises the crystal form characterized by at least one of the following:

a) single crystal structure having unit cell parameters substantially equal to

Crystal system, space group	Triclinic, P1	
Unit cell dimensions	a = 6.53 ± 0.10 Å	alpha = $92.8 \pm 1.0^\circ$
	b = 13.06 ± 0.10 Å	beta = $95.5 \pm 1.0^\circ$
	c = 14.04 ± 0.10 Å	gamma = $93.0 \pm 1.0^\circ$
Volume	$1189(20)$ Å ³	
Density (calculated)	1.239 g/cm ³	
Temperature	room temperature	

wherein measurement of the single crystal structure is at room temperature;

b) a powder x-ray diffraction pattern substantially the same as shown in FIG. 1;

c) a powder x-ray diffraction pattern comprising 2 or more peaks at 2θ values selected from 6.4 ± 0.2 , 6.8 ± 0.2 , 9.6 ± 0.2 , 13.6 ± 0.2 , 15.7 ± 0.2 , 18.2 ± 0.2 , 19.9 ± 0.2 , 21.6 ± 0.2 , 24.8 ± 0.2 and 26.8 ± 0.2 (obtained at room temperature and CuKα $\lambda = 1.5418$ Å);

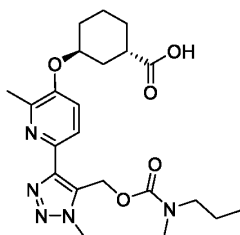
d) a powder x-ray diffraction pattern comprising 3 or more peaks at 2θ values selected from 6.4 ± 0.2 , 6.8 ± 0.2 , 9.6 ± 0.2 , 13.6 ± 0.2 , 14.1 ± 0.2 , 14.5 ± 0.2 , 14.7 ± 0.2 , 15.7 ± 0.2 , 18.2 ± 0.2 , 18.7 ± 0.2 , 19.2 ± 0.2 , 19.9 ± 0.2 , 20.5 ± 0.2 , 21.6 ± 0.2 , 22.5 ± 0.2 , 23.1 ± 0.2 , 24.1 ± 0.2 , 24.8 ± 0.2 , 25.6 ± 0.2 , 26.8 ± 0.2 , 27.1 ± 0.2 and 27.8 ± 0.2 (obtained at room temperature and CuKα $\lambda = 1.5418$ Å);

e) a differential scanning calorimetry thermogram substantially similar to the one as shown in FIG. 2;

f) a differential scanning calorimetry thermogram with an endotherm having an onset at about 152 °C; and/or

g) a thermal gravimetric analysis thermogram substantially similar to the one as shown in FIG. 3.

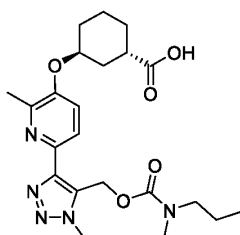
54. The method of any one of claims 1 to 53, wherein the subject experiences a smaller decline in forced vital capacity (FVC) after a treatment period compared to an untreated subject.
55. The method of any one of claims 1 to 54, wherein the subject experiences a greater time to first disease progression event after a treatment period than an untreated subject, wherein the first disease progression event is selected from:
 - absolute predicted forced vital capacity (ppFVC) decline of $\geq 10\%$ from baseline;
 - acute exacerbation of lung fibrosis;
 - respiratory-related hospitalization; and
 - all-cause mortality.
56. The method of any one of claims 1 to 55, wherein the subject experiences a smaller increase in cough domain score as measured by the Living with Pulmonary Fibrosis (L-PF) questionnaire over a treatment period than an untreated subject.
57. The method of any one of claims 1 to 56, wherein the subject experiences a smaller increase in dyspnea score as measured by the Living with Pulmonary Fibrosis (L-PF) questionnaire over a treatment period than an untreated subject.
58. In a method of treating a subject with an LPA₁ antagonist for treating interstitial lung disease, the improvement comprising: reducing the incidence of cardiovascular adverse events in the subject receiving the LPA₁ antagonist by use of an initial dose escalation regimen comprising administering the LPA₁ antagonist to the subject at a daily dosage lower than the standard daily dosage during an initial period of treatment then increasing the dosage to the standard daily dosage of the LPA₁ antagonist.
59. The method of claim 58, wherein the LPA₁ antagonist is Compound A:



Compound A;

or a pharmaceutically acceptable salt thereof, and the standard daily dosage is about 120 mg/day of Compound A or an equivalent amount of a pharmaceutically acceptable salt thereof.

60. The method of claim 58 or 59, wherein the interstitial lung disease is idiopathic pulmonary fibrosis (IPF).
61. The method of claim 58 or 59, wherein the interstitial lung disease is progressive pulmonary fibrosis (PPF).
62. Use of an LPA₁ antagonist for treating interstitial lung disease in a subject in need thereof, wherein the LPA₁ antagonist is administered to the subject at a daily dosage lower than the standard daily dosage during an initial period of treatment then the dosage is increased to the standard daily dosage of the LPA₁ antagonist.
63. The use of claim 62, wherein the LPA₁ antagonist is Compound A:



Compound A;

or a pharmaceutically acceptable salt thereof, for treating interstitial lung disease and the standard daily dosage is about 120 mg/day of Compound A, or an equivalent amount of a pharmaceutically acceptable salt thereof.

64. The use of claim 62 or 63, wherein the interstitial lung disease is idiopathic pulmonary fibrosis (IPF).
65. The use of claim 62 or 63, wherein the interstitial lung disease is progressive pulmonary fibrosis (PPF).