PCT REQUEST

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0	**For receiving Office use only**	
0-1	International Application No.	
0-2	International Filing Date	
0-3	Name of receiving Office and "PCT International Application"	

0-4	**Form PCT/RO/101 PCT Request**	
0-4-1	Prepared Using	**ePCT-Filing for data package download Version 4.10.009 MT/FOP 20221019/1.1**
0-5	**Petition**	
	The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty	
0-6	**Receiving Office (specified by the applicant)**	**United States Patent and Trademark Office (USPTO) (RO/US)**
0-7	**Applicant's or agent's file reference**	**72MM-341180-WO**
I	**Title of Invention**	**METHODS FOR TREATING SYSTEMIC LUPUS ERYTHEMATOSUS**
II	**Applicant**	
II-1	This person is	**Applicant only**
II-2	Applicant for	**All designated States**
II-4	Name	**ARIA PHARMACEUTICALS, INC.**
II-5	Address	**265 Cambridge Avenue, #60099 Palo Alto, California 94306 United States of America**
II-6	State of nationality	**US**
II-7	State of residence	**US**
III-1	**Applicant and/or inventor**	
III-1-1	This person is	**Inventor only**
III-1-3	Inventor for	**All designated States**
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III-3	**Applicant and/or inventor**	
III-3-1	This person is	**Inventor only**
III-3-3	Inventor for	**All designated States**
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III-4	**Applicant and/or inventor**	
III-4-1	This person is	**Inventor only**
III-4-3	Inventor for	**All designated States**
III-4-4	Name (LAST, First)	**PANDEY, Anjali**
III-4-5	Address	**c/o Aria Pharmaceuticals, Inc. 265 Cambridge Avenue, #60099 Palo Alto, California 94306 United States of America**
IV-1	**Agent or common representative; or address for correspondence** The person identified below is hereby/ has been appointed to act on behalf of the applicant(s) before the competent International Authorities as:	**Agent**
IV-1-1	Name (LAST, First)	**TANNER, Lorna L.**
IV-1-2	Address	**SHEPPARD MULLIN RICHTER & HAMPTON LLP 650 Town Center Drive, 10th Floor Costa Mesa, California 92626-1993 United States of America**
IV-1-3	Telephone No.	**650-815-2600**
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IV-1-5	e-mail	**svipdocketing@sheppardmullin.com**
IV-1-5(a)	E-mail authorization The receiving Office, the International Searching Authority, the International Bureau and the International Preliminary Examining Authority are authorized to use this e-mail address, if the Office or Authority so wishes, to send notifications issued in respect of this international application:	**as advance copies followed by paper notifications**
IV-1-6	Agent's registration No.	**50,782**
IV-2	**Additional agent(s)**	**additional agent(s) with same address as first named agent**
IV-2-1	Name(s)	**CHANG, Young(80,093); HIRAYAMA, Lacie C.(63,866); LEE, Nathan(75,560); NEMIROW, Joy L.(67,163); NIE, Alex Y. (60,523); XIE, Xin(70,890)**
V	**DESIGNATIONS**	
V-1	**The filing of this request constitutes under Rule 4.9(a), the designation of all Contracting States bound by the PCT on the international filing date, for the grant of every kind of protection available and, where applicable, for the grant of both regional and national patents.**	

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VI-1	**Priority claim of earlier national application**		
VI-1-1	Filing date	**27 October 2021 (27.10.2021)**	
VI-1-2	Number	**63/272,560**	
VI-1-3	Country or Member of WTO	**US**	
VI-2	**Priority document request**		
	The International Bureau is requested to obtain from a digital library a certified copy of the earlier application(s) identified above as item(s), using, where applicable, the access code(s) indicated:	**VI-1 Access code: 3148**	
VI-3	**Incorporation by reference :**		
	where an element of the international application referred to in Article 11(1)(iii)(d) or (e) or a part of the description, claims or drawings referred to in Rule 20.5(a), or an element or part of the description, claims or drawings referred to in Rule 20.5bis(a) is not otherwise contained in this international application but is completely contained in an earlier application whose priority is claimed on the date on which one or more elements referred to in Article 11(1)(iii) were first received by the receiving Office, that element or part is, subject to confirmation under Rule 20.6, incorporated by reference in this international application for the purposes of Rule 20.6.		
VII-1	**International Searching Authority Chosen**	**European Patent Office (EPO) (ISA/EP)**	
VIII	**Declarations**	Number of declarations	
VIII-1	Declaration as to the identity of the inventor	-	
VIII-2	Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent	-	
VIII-3	Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application	1	
VIII-4	Declaration of inventorship (only for the purposes of the designation of the United States of America)	-	
VIII-5	Declaration as to non-prejudicial disclosures or exceptions to lack of novelty	-	

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VIII-3-1	**Declaration: Entitlement to claim priority** Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application specified below, where the applicant is not the applicant who filed the earlier application or where the applicant's name has changed since the filing of the earlier application (Rules 4.17(iii) and 51bis.1(a)(iii)) Name	**In relation to this international application** **ARIA PHARMACEUTICALS, INC.** **is entitled to claim priority of earlier application No. US 63/272,560 by virtue of the following:**
VIII-3-1 (iv)		**an assignment from HAKIM, Isaac to ARIA PHARMACEUTICALS, INC., dated 14 October 2022 (14.10.2022)**
VIII-3-1 (iv)		**an assignment from DAUGHERTY, Aaron to ARIA PHARMACEUTICALS, INC., dated 14 October 2022 (14.10.2022)**
VIII-3-1 (iv)		**an assignment from MUJAHID, Sana to ARIA PHARMACEUTICALS, INC., dated 14 October 2022 (14.10.2022)**
VIII-3-1 (iv)		**an assignment from PANDEY, Anjali to ARIA PHARMACEUTICALS, INC., dated 20 October 2022 (20.10.2022)**

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IX	Check list	Number of sheets	Electronic file(s) attached
IX-1	Request (including declaration sheets)	**5**	✓
IX-2	Description	**24**	✓
IX-3	Claims	**3**	✓
IX-4	Abstract	**1**	✓
IX-5	Drawings	**6**	✓
IX-6a	Sequence listing part of the description	**-**	**-**
IX-7	TOTAL	**39**	
	Accompanying Items	Paper document(s) attached	Electronic file(s) attached
IX-8	Fee calculation sheet	**-**	✓
IX-20	**Figure of the drawings which should accompany the abstract**	**1**	
IX-21	**Language of filing of the international application**	**English**	
X-1	**Signature of applicant, agent or common representative**	**/Lorna L. TANNER, Reg. No. 50,782/**	
X-1-1	Name (LAST, First)	**TANNER, Lorna L.**	
X-1-3	Capacity (if such capacity is not obvious from reading the request)	**Agent**	

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10-1	**Date of actual receipt of the purported international application**	
10-2	**Drawings:**	
10-2-1	Received	
10-2-2	Not received	
10-3	**Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application**	
10-4	**Date of timely receipt of the required corrections under PCT Article 11(2)**	
10-5	**International Searching Authority**	**ISA/EP**
10-6	**Transmittal of search copy delayed until search fee is paid**	

FOR INTERNATIONAL BUREAU USE ONLY

11-1	**Date of receipt of the record copy by the International Bureau**	

METHODS FOR TREATING SYSTEMIC LUPUS ERYTHEMATOSUS

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit under 35 U.S.C. §119(e) to U.S. Provisional Application Numbers 63/272,560, filed October 27, 2021, which is incorporated by reference in its entirety.

FIELD

[0002] Provided is a method for treating systemic lupus erythematosus (SLE) in a patient in need thereof comprising administering a therapeutically effective amount of a leucine-rich repeat kinase 2 (LRRK2) inhibitor.

BACKGROUND

[0003] Systemic lupus erythematosus (SLE) is an autoimmune disease in which the immune system attacks its own tissues, causing widespread inflammation and tissue damage in the affected organs. It can affect the joints, skin, brain, lungs, kidneys, and blood vessels. The causes of SLE are unknown, but are believed to be linked to environmental, genetic, and hormonal factors.

[0004] SLE treatment consists primarily of immunosuppressive drugs that inhibit activity of the immune system. Hydroxychloroquine and corticosteroids (e.g., prednisone) are often used to treat SLE. The FDA approved belimumab in 2011, the first new drug for SLE in more than 50 years. As there is no known cure for SLE, treatment generally involves identifying and treating the signs and symptoms of each individual patient. The signs and symptoms of SLE depend on which body systems are affected by the disease, and most commonly include fatigue, fever, joint pain, stiffness and swelling, rashes, such as a butterfly-shaped rash on the face that covers the cheeks and bridge of the nose, or rashes elsewhere on the body, skin lesions that appear or worsen with sun exposure, fingers and toes that turn white or blue when exposed to cold or during stressful periods, shortness of breath, chest pain, dry eyes, headaches, confusion, or memory loss. Other symptoms can include sun sensitivity, oral ulcers, arthritis, lung problems, heart problems, kidney problems, seizures, psychosis, and blood cell and immunological abnormalities.

[0005] Medications most commonly used to control lupus include nonsteroidal anti-inflammatory drugs (NSAIDs), antimalarial drugs, corticosteroids, immunosuppressants, and biologics. However, each can have side effects when taken chronically and/or in high doses.

[0006] Over-the-counter NSAIDs, such as naproxen sodium (Aleve) and ibuprofen (Advil, Motrin IB, others), may be used to treat pain, swelling and fever associated with lupus, with stronger NSAIDs available by prescription. Side effects of NSAIDs may include stomach bleeding, kidney problems, and an increased risk of heart problems.

[0007] Medications commonly used to treat malaria, such as hydroxychloroquine (Plaquenil), affect the immune system and can help decrease the risk of lupus flares. Side effects can include stomach upset

and, very rarely, damage to the retina of the eye. Regular eye exams are recommended when taking these medications.

[0008] Prednisone and other types of corticosteroids can counter the inflammatory symptoms of lupus. High doses of steroids such as methylprednisolone (Medrol) are often used to control serious disease that involves the kidneys and brain. Side effects include weight gain, easy bruising, thinning bones, high blood pressure, diabetes, and increased risk of infection. The risk of side effects increases with higher doses and longer term therapy.

[0009] Drugs that suppress the immune system may be helpful in serious cases of lupus. Examples include azathioprine (Imuran, Azasan), mycophenolate (Cellcept), methotrexate (Trexall, Xatmep, others), cyclosporine (Sandimmune, Neoral, Gengraf), voclosporin (Lupkynis), and leflunomide (Arava). Potential side effects may include an increased risk of infection, liver damage, decreased fertility, and an increased risk of cancer.

[0010] The biologic belimumab (Benlysta) administered intravenously, also reduces lupus symptoms in some people. Side effects include nausea, diarrhea, and infections. Rarely, worsening of depression can occur. Rituximab (Rituxan, Truxima), also a biologic, may be beneficial for some people in whom other medications have not helped. Side effects include allergic reaction to the intravenous infusion and infections.

[0011] Among some adults, having a period of SLE symptoms, referred to as flares, may happen every so often, sometimes even years apart, and go away at other times (i.e., remission). However, other adults may experience SLE flares more frequently throughout their life.

[0012] Given the limited treatments available, as well as the potential for side effects from these treatments, people with lupus seek alternative or complementary medicine. Thus, a need exists for therapeutic agents for treating systemic lupus erythematosus (SLE).

SUMMARY

[0013] Systemic lupus erythematosus (SLE) is a prototypic autoimmune disease characterized by the presence of pathogenic autoantibodies associated with polyclonal B cell hyperreactivity causing a person's immune system to attack the body's own organs and tissues. Almost every system of the body can be affected by SLE.

[0014] It has been discovered that a LRRK2 inhibitor was effective at treating SLE in a mouse model, as evidence by a preservation of kidney function in test subjects with hyperactive, self-reactive B and T cells, autoantibodies directed against nuclear antigens, and defective clearance of immune complexes. Subjects displayed decreased production of double-stranded DNA antibody (anti-dsDNA antibody), decreased concentration of blood urea nitrogen (BUN), and decreased proteinuria compared with a control group. This indicates a decrease in damage to the kidneys of the subjects associated with

the uncontrolled inflammation and immune response to apoptotic cell debris associated with dysfunctional immune responses, such as SLE.

[0015] Provided herein are methods for treating systemic lupus erythematosus (SLE), comprising administering to a patient in need thereof, a therapeutically effective amount of a leucine-rich repeat kinase 2 (LRRK2) inhibitor.

[0016] Provided herein are methods for treating systemic lupus erythematosus (SLE), comprising administering to a patient in need thereof, a therapeutically effective amount of Compound 1, or a pharmaceutically acceptable salt thereof.

[0017] Also provided herein are methods for treating systemic lupus erythematosus (SLE), comprising administering to a patient in need thereof, a pharmaceutical composition, comprising a therapeutically effective amount of a leucine-rich repeat kinase 2 (LRRK2) inhibitor, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

[0018] Also provided herein are methods for treating systemic lupus erythematosus (SLE), comprising administering to a patient in need thereof, a pharmaceutical composition, comprising a therapeutically effective amount of Compound 1, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

[0019] Also provided herein are methods for treating systemic lupus erythematosus (SLE), comprising administering an effective amount of a leucine-rich repeat kinase 2 (LRRK2) inhibitor to a patient in need thereof, wherein said patient also suffers from Sjogren's syndrome, antiphospholipid syndrome, thyroiditis, hemolytic anemia, or idiopathic thrombocytopenia purpura.

[0020] Also provided herein are methods for treating systemic lupus erythematosus (SLE), comprising administering an effective amount of Compound 1, or a pharmaceutically acceptable salt thereof, to a patient in need thereof, wherein said patient also suffers from Sjogren's syndrome, antiphospholipid syndrome, thyroiditis, hemolytic anemia, or idiopathic thrombocytopenia purpura.

[0021] Also provided herein are methods for improving kidney function, comprising administering to a patient in need thereof, a therapeutically effective amount of Compound 1, or a pharmaceutically acceptable salt thereof.

[0022] Also provided herein are methods for inhibiting the production of double-stranded DNA antibody (anti-dsDNA antibody), comprising administering to a patient in need thereof, a therapeutically effective amount of Compound 1, or a pharmaceutically acceptable salt thereof.

[0023] Also provided herein are methods for decreasing the concentration of blood urea nitrogen (BUN), comprising administering to a patient in need thereof, a therapeutically effective amount of Compound 1, or a pharmaceutically acceptable salt thereof.

[0024] Also provided herein are methods for decreasing proteinuria, comprising administering to a patient in need thereof, a therapeutically effective amount of Compound 1, or a pharmaceutically acceptable salt thereof.

[0025] Also provided herein are methods for treating systemic lupus erythematosus (SLE), comprising administering to a patient in need thereof, a therapeutically effective amount of Compound 1, or a pharmaceutically acceptable salt thereof, wherein the treating comprises inhibiting, lessening, or delaying the onset or progression of, fatigue, fever, joint pain, joint stiffness, joint swelling, rashes, skin lesions, shortness of breath, chest pain, dry eyes, headaches, confusion, memory loss, sun sensitivity, oral ulcers, arthritis, lung damage, heart problems, kidney damage, lupus nephritis, lymphadenopathy, seizures, psychosis, blood cell abnormalities, or immunological abnormalities.

[0026] Also provided herein are methods for treating systemic lupus erythematosus (SLE), comprising administering to a patient in need thereof, a therapeutically effective amount of Compound 1, or a pharmaceutically acceptable salt thereof, wherein the treating comprises inhibiting, lessening, or delaying the onset or progression of, skin lesions, lymphadenopathy, kidney damage, lupus nephritis, or inflammation.

[0027] Also provided herein are methods for treating systemic lupus erythematosus (SLE), comprising administering to a patient in need thereof, a therapeutically effective amount of Compound 1, or a pharmaceutically acceptable salt thereof, wherein the patient is experiencing a lupus flare.

BRIEF DESCRIPTION OF THE FIGURES

[0028] FIG. 1 shows the lymphadenopathy scores for mouse test groups over the course of study, with a group treated only with oral gavage vehicle comprising 0.5% carboxymethyl cellulose (CMC) and 5% DMSO, a reference group which received cyclophosphamide (Cyc), and a group treated with Compound 1. The group treated with Compound 1 displayed a decrease in lymphadenopathy score at days 42, 48, and 56.

[0029] FIG. 2 shows the skin lesion scores for mouse test groups over the course of study, with a group treated only with oral gavage vehicle comprising 0.5% carboxymethyl cellulose (CMC) and 5% DMSO, a reference group which received cyclophosphamide (Cyc), and a group treated with Compound 1. The group treated with Compound 1 displayed a statistically significant decrease (p value = < 0.0001) in skin lesions.

[0030] FIG. 3 shows the lymph node weight of samples collected from a group treated only with oral gavage vehicle comprising 0.5% carboxymethyl cellulose (CMC) and 5% DMSO, a reference group which received cyclophosphamide (Cyc), and a group treated with Compound 1. The group treated with Compound 1 exhibited a reduction in the inguinal lymph node weight, but it was not statistically significant ($p = 0.06$) when compared to animals treated with only vehicle.

[0031] FIG. 4 shows the proteinuria scores for mouse test groups over the course of study, with a group treated only with oral gavage vehicle comprising 0.5% carboxymethyl cellulose (CMC) and 5% DMSO, a reference group which received cyclophosphamide (Cyc), and a group treated with Compound 1. The group treated with Compound 1 displayed a non-statistical decrease in urine protein content when compared to that seen in the group treated with only vehicle.

[0032] FIG. 5 shows the blood urea nitrogen for samples collected from a group treated only with oral gavage vehicle comprising 0.5% carboxymethyl cellulose (CMC) and 5% DMSO, a reference group which received cyclophosphamide (Cyc), and a group treated with Compound 1. The group treated with Compound 1 showed a similar decrease ($p = < 0.05$) in blood urea content as was observed in the group treated with cyclophosphamide.

[0033] FIG. 6 shows the anti-dsDNA IgG response in a group treated only with oral gavage vehicle comprising 0.5% carboxymethyl cellulose (CMC) and 5% DMSO, a reference group which received cyclophosphamide (Cyc), and a group treated with Compound 1. The group treated with Compound 1 displayed comparable levels of anti-dsDNA antibodies to those treated with only vehicle. The cyclophosphamide test group showed a non-statistically significant reduction in anti-dsDNA antibodies.

[0034] FIG. 7 shows tubule basophilia scores for samples collected from a group treated only with oral gavage vehicle comprising 0.5% carboxymethyl cellulose (CMC) and 5% DMSO, a reference group which received cyclophosphamide (Cyc), and a group treated with Compound 1. The group treated with Compound 1 displayed a statistically significant decrease ($p = 0.01$-0.05) in tubule basophilia histology score as compared to those treated with only vehicle.

[0035] FIG. 8 shows tubule dilation/casts scores for samples collected from a group treated only with oral gavage vehicle comprising 0.5% carboxymethyl cellulose (CMC) and 5% DMSO, a reference group which received cyclophosphamide (Cyc), and a group treated with Compound 1. The group treated with Compound 1 displayed a reduction in score with $p = 0.1$.

[0036] FIG. 9 shows glomerulonephritis scores for samples collected from a group treated only with oral gavage vehicle comprising 0.5% carboxymethyl cellulose (CMC) and 5% DMSO, a reference group which received cyclophosphamide (Cyc), and a group treated with Compound 1. The group treated with Compound 1 displayed a reduction in score with $p = 0.1$.

[0037] FIG. 10 shows chronic interstitial inflammation scores for samples collected from a group treated only with oral gavage vehicle comprising 0.5% carboxymethyl cellulose (CMC) and 5% DMSO, a reference group which received cyclophosphamide (Cyc), and a group treated with Compound 1. The group treated with Compound 1 displayed a statistically significant reduction ($p = 0.01$-0.05) in chronic interstitial inflammation, as compared to those treated with only vehicle.

[0038] FIG. 11 shows chronic papillary inflammation scores for samples collected from a group treated only with oral gavage vehicle comprising 0.5% carboxymethyl cellulose (CMC) and 5% DMSO,

a reference group which received cyclophosphamide (Cyc), and a group treated with Compound 1. The group treated with Compound 1 displayed a reduction in chronic papillary inflammation, when compared to those treated with only vehicle.

[0039] FIG. 12 shows the summation of histology scores for a group treated only with oral gavage vehicle comprising 0.5% carboxymethyl cellulose (CMC) and 5% DMSO, a reference group which received cyclophosphamide (Cyc), and a group treated with Compound 1. The group treated with Compound 1 displayed an overall statistically significant reduction ($p = < 0.01\text{-}0.05$) in histology scores, as compared to those treated only with vehicle.

DETAILED DESCRIPTION

Definitions

[0040] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of ordinary skill in the art. As used herein, the below terms have the following meanings unless specified otherwise. Any methods, devices, and materials similar or equivalent to those described herein can be used in the practice of the compositions and methods described herein. The following definitions are provided to facilitate understanding of certain terms used frequently herein and are not meant to limit the scope of the present disclosure. All references referred to herein are incorporated by reference in their entirety.

[0041] It is noted here that as used in this specification and the appended claims, the singular forms "a" "an" and "the" and the like include plural referents unless the context clearly dictates otherwise.

[0042] The term "about" or "approximately" means within ± 30%, 20%, 15%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1%, 0.5%, or 0.05% of a given value or range. In some embodiments, "about" means ± 5% of a given value or range. In some embodiments, "about" means ± 4% of a given value or range. In some embodiments, "about" means ± 3% of a given value or range. In some embodiments, "about" means ± 2% of a given value or range. In some embodiments, "about" means ± 1% of a given value or range. In another embodiment, about means ± 0.5% of a given value or range. In some embodiments, "about" means ± 0.05% of a given value or range.

[0043] "Pharmaceutically acceptable" or "physiologically acceptable" refer to compounds, salts, compositions, dosage forms, and other materials which are useful in preparing a pharmaceutical composition that is suitable for human or veterinary pharmaceutical use.

[0044] The term "pharmaceutically acceptable salt" of a given compound refers to salts that retain the biological effectiveness and properties of the given compound, and which are not biologically or otherwise undesirable. "Pharmaceutically acceptable salts" or "physiologically acceptable salts" include, for example, salts with inorganic acids and salts with an organic acid. In addition, if the compounds described herein are obtained as an acid addition salt, the free base can be obtained by basifying a

solution of the acid salt. Conversely, if the product is a free base, an addition salt, particularly a pharmaceutically acceptable addition salt, may be produced by dissolving the free base in a suitable organic solvent and treating the solution with an acid, in accordance with conventional procedures for preparing acid addition salts from base compounds. Those skilled in the art will recognize various synthetic methodologies that may be used to prepare nontoxic pharmaceutically acceptable addition salts. Pharmaceutically acceptable acid addition salts may be prepared from inorganic and organic acids. Salts derived from inorganic acids include hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like. Salts derived from organic acids include acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, malic acid, malonic acid, succinic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluene-sulfonic acid, salicylic acid, and the like. Likewise, pharmaceutically acceptable base addition salts can be prepared from inorganic and organic bases. Salts derived from inorganic bases include, by way of example only, sodium, potassium, lithium, ammonium, calcium, and magnesium salts. Salts derived from organic bases include, but are not limited to, salts of primary, secondary, and tertiary amines. Specific examples of suitable amines include, by way of example only, isopropylamine, trimethyl amine, diethyl amine, tri(iso-propyl) amine, tri(n-propyl) amine, ethanolamine, 2-dimethylaminoethanol, piperazine, piperidine, morpholine, N-ethylpiperidine, and the like.

[0045] As used herein, the term "administration" refers to introducing an agent into a patient. For example, a therapeutic amount can be administered to the patient, which can be determined by the treating physician, medical professional, or the like. In some embodiments, an oral route of administration is preferred. The related terms and phrases "administering" and "administration of," when used in connection with a compound or tablet (and grammatical equivalents) refer both to direct administration, which may be administration to a patient by a medical professional or by self-administration by the patient, and/or to indirect administration, which may be the act of prescribing a drug. Administration entails delivery to the patient of the drug.

[0046] The term "dose" or "dosage" refers to the total amount of an active agent (e.g., a LRRK2 inhibitor or a pharmaceutically acceptable salt thereof) administered to a patient in a single day (24-hour period). The desired dose can be administered once daily. In some embodiments, the desired dose may be administered in one, two, three, four or more sub-doses at appropriate intervals throughout the day, where the cumulative amount of the sub-doses equals the amount of the desired dose administered in a single day. The terms "dose" and "dosage" are used interchangeably herein.

[0047] As used herein, "therapeutically effective amount" or "therapeutic amount" refers to an amount of a drug or an agent (e.g., a LRRK2 inhibitor or a pharmaceutically acceptable salt thereof) that when administered to a patient suffering from a condition, will have the intended therapeutic effect, e.g., alleviation, amelioration, palliation or elimination of one or more manifestations of the condition in the patient. The full therapeutic effect does not necessarily occur by administration of one dose, and can

occur only after administration of a series of doses and can be administered in one dose form or multiples thereof. Thus, a therapeutically effective amount may be administered in one or more administrations.

[0048] As used herein, the term "patient" refers to a mammal, such as a human, bovine, rat, mouse, dog, monkey, ape, goat, sheep, cow, or deer. A patient as described herein can be a human.

[0049] As used herein, "treatment," "treating," and "treat" are defined as acting upon a disease, disorder, or condition with an agent to reduce or ameliorate the harmful or any other undesired effects of the disease, disorder, or condition and/or its symptoms. Treatment, as used herein, covers the treatment of a human patient, and includes: (a) reducing the risk of occurrence of the condition in a patient determined to be predisposed to the disease but not yet diagnosed as having the condition, (b) impeding the development of the condition, and/or (c) relieving the condition, i.e., causing regression of the condition and/or relieving one or more symptoms of the condition.

Methods of Treatment

[0050] Provided herein are methods for treating systemic lupus erythematosus (SLE), comprising administering a therapeutically effective amount of a leucine-rich repeat kinase 2 (LRRK2) inhibitor to a patient in need thereof.

[0051] In some embodiments, the LRRK2 inhibitor is Compound 1, MLi-2, IKK 16, IKK 16 hydrochloride, PF-06447475, PFE-360, GNE-7915, GNE-7915 tosylate, CZC-54252, CZC-54252 hydrochloride, GNE0877, LRRK2-IN-1, TAE684, G1023, BMPPB-32, PF-06371900, sunitinib, Nov-LRRK2-11, *N*-(2-methoxyethyl)-3-(phenylsulfonamido)benzamide, HG-10-102-01, GNE-9605, JH-II-127, CZC-25146, CZC-25146 hydrochloride, LRRK2 inhibitor 1, DNL201, or DNL151. In some embodiments, the LRRK2 inhibitor is Compound 1. In some embodiments, the LRRK2 inhibitor is MLi-2. In some embodiments, the LRRK2 inhibitor is IKK 16. In some embodiments, the LRRK2 inhibitor is IKK 16 hydrochloride. In some embodiments, the LRRK2 inhibitor is PF-06447475. In some embodiments, the LRRK2 inhibitor is PFE-360. In some embodiments, the LRRK2 inhibitor is GNE-7915. In some embodiments, the LRRK2 inhibitor is GNE-7915 tosylate. In some embodiments, the LRRK2 inhibitor is CZC-54252. In some embodiments, the LRRK2 inhibitor is CZC-54252 hydrochloride. In some embodiments, the LRRK2 inhibitor is GNE0877. In some embodiments, the LRRK2 inhibitor is LRRK2-IN-1. In some embodiments, the LRRK2 inhibitor is TAE684. In some embodiments, the LRRK2 inhibitor is G1023. In some embodiments, the LRRK2 inhibitor is BMPPB-32. In some embodiments, the LRRK2 inhibitor is PF-06371900. In some embodiments, the LRRK2 inhibitor is sunitinib. In some embodiments, the LRRK2 inhibitor is Nov-LRRK2-11. In some embodiments, the LRRK2 inhibitor is *N*-(2-methoxyethyl)-3-(phenylsulfonamido)benzamide. In some embodiments, the LRRK2 inhibitor is HG-10-102-01. In some embodiments, the LRRK2 inhibitor is GNE-9605. In some embodiments, the LRRK2 inhibitor is JH-II-127. In some embodiments, the LRRK2 inhibitor is CZC-25146. In some embodiments, the LRRK2 inhibitor is CZC-25146 hydrochloride. In

some embodiments, the LRRK2 inhibitor is LRRK2 inhibitor 1. In some embodiments, the LRRK2 inhibitor is DNL201. In some embodiments, the LRRK2 inhibitor is DNL151. In some embodiments, the LRRK2 inhibitor is EB-42486. In some embodiments, the LRRK2 inhibitor is G2019S-LRRK2 inhibitor 38. In some embodiments, the LRRK2 inhibitor is G2019S-LRRK2 inhibitor 22. In some embodiments, the LRRK2 inhibitor is LRRK2 inhibitor 18. In some embodiments, the LRRK2 inhibitor is LRRK2-IN-3. In some embodiments, the LRRK2 inhibitor is LRRK2-IN-2. In some embodiments, the LRRK2 inhibitor is LRRK2-IN-4. In some embodiments, the LRRK2 inhibitor is XL01126. In some embodiments, the LRRK2 inhibitor is PF-06456384.

[0052] Also provided herein are methods of treating systemic lupus erythematosus (SLE), comprising administering a composition, comprising a therapeutically effective amount of a leucine-rich repeat kinase 2 (LRRK2) inhibitor and a pharmaceutically acceptable carrier, to a patient in need thereof.

[0053] Also provided herein are methods of improving kidney function, comprising administering a therapeutically effective amount of a leucine-rich repeat kinase 2 (LRRK2) inhibitor to a patient in need thereof.

[0054] Also provided herein is a method for inhibiting the production of double-stranded DNA antibody (anti-dsDNA antibody), comprising administering a therapeutically effective amount of a leucine-rich repeat kinase 2 (LRRK2) inhibitor to a patient in need thereof.

[0055] Also provided herein is a method for decreasing the concentration of blood urea nitrogen (BUN), comprising administering a therapeutically effective amount of a leucine-rich repeat kinase 2 (LRRK2) inhibitor to a patient in need thereof.

[0056] Also provided is a method of decreasing proteinuria, comprising administering a therapeutically effective amount of a leucine-rich repeat kinase 2 (LRRK2) inhibitor to a patient in need thereof.

[0057] In some embodiments, the therapeutically effective amount of a leucine-rich repeat kinase 2 inhibitor treats systemic lupus erythematosus in a patient in need thereof by suppressing inflammation.

[0058] In some embodiments, the therapeutically effective amount of a leucine-rich repeat kinase 2 inhibitor treats systemic lupus erythematosus in a patient in need thereof by inducing phagocyte autophagy.

[0059] In some embodiments, the patient is female. In some embodiments, the patient is less than 50 years of age.

[0060] In some embodiments, the patient also suffers from other autoimmune conditions, like Sjogren's syndrome, antiphospholipid syndrome, thyroiditis, hemolytic anemia, and idiopathic thrombocytopenia purpura. In some embodiments, the patient does not also suffer from other autoimmune conditions.

Leucine-Rich Repeat Kinase 2 (LRRK2) Inhibitors

[0061] Leucine-rich repeat kinase 2 (LRRK2) inhibitors are a class of compounds capable of suppressing inflammation and inducing phagocyte autophagy involved throughout the innate and adaptive immune response. Similarly, LRRK2 inhibitors are capable of inhibiting macrophage differentiation, infiltration, and activation, as well as autophagy in B cells and macrophages. Monocyte recruitment and differentiation of IL-1, 6, 12, and TNF-α secreting macrophages are also decreased by LRRK2 inhibitors. Further, LRRK2 inhibitors have been shown to inhibit pro-inflammatory signaling, as well as cytokine expression and oxidative stress, while decreasing p62 expression and NF-κB activity. LRRK2 inhibition can block or reverse phenotypic changes associated with SLE, while maintaining excellent tolerability.

[0062] LRRK2 inhibitors are described in at least U.S. Pat. Nos 8,206,942, 8,404,677, 8,629,132, 9,156,845, 9,365,551, 9,493,452, 9,499,542, 9,642,855, 9,675,594, 9,695,171, 10,023,579, 10,039,753, 10,087,186, 10,294,235, 10,618,901, 10,913,744, 10,975,081, 11,028,080, and 11,034,696, and published WIPO applications WO 2009/030270, WO 2009/127642, WO 2010/080712, WO 2010/08579, WO 2011/038572, WO 2011/053861, WO 2011/057204, WO 2011/060295, WO 2011/106168, WO 2011/141756, WO 2011/151360, WO 2012/028629, WO 2012/038743, WO 2012/058193, WO 2012/062783, WO 2012/118679, WO 2012/135631, WO 2012/143143, WO 2012/143144, WO 2012/162254, WO 2012/178015, WO 2013/046029, WO 2013/139882, WO 2013/164321, WO 2013/166276, and WO 2014/001973, which are incorporated herein by reference. Examples of LRRK2 inhibitors include, but are not limited to, Compound 1, MLi-2, IKK 16, PF-06447475, PFE-360, GNE-7915, CZC-54252, GNE0877, LRRK2-IN-1, TAE684, G1023, BMPPB-32, PF-06371900, sunitinib, Nov-LRRK2-11, *N*-(2-methoxyethyl)-3-(phenylsulfonamido)benzamide, HG-10-102-01, GNE-9605, JH-II-127, CZC-25146, LRRK2 inhibitor 1, DNL201, or DNL151.

[0063] LRRK2 inhibitors can be identified using a homogeneous time-resolved fluorescence (HTRF) assay that measures the inhibition of phosphorylation of the peptide substrate LRRKtide by baculoviral-derived recombinant 6His-Tev-LRRK2. Kinase selectivity can be assessed using standard radioactivity-based enzymatic assays against a panel of various kinases. While the direct phosphorylation substrates of LRRK2 in a cellular context are not yet validated, determining the phosphorylation of two residues known to be dependent on LRRK2 kinase activity, Ser910 and Ser935, provides insight into putative inhibitory activity of a compound in HEK293 cells transfected with LRRK2. Compounds can also be tested against endogenous phosphorylation of these two residues in human lymphoblastoid cells derived from a Parkinson's disease patient homozygous for the LRRK2 G2019S variant.

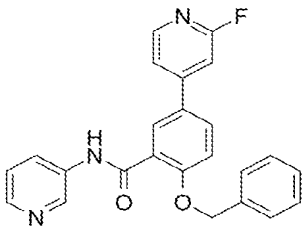
[0064] In certain embodiments, the LRRK2 inhibitor is Compound 1, MLi-2, IKK 16, PF-06447475, PFE-360, GNE-7915, CZC-54252, GNE0877, LRRK2-IN-1, TAE684, G1023, BMPPB-32, PF-06371900, sunitinib, Nov-LRRK2-11, *N*-(2-methoxyethyl)-3-(phenylsulfonamido)benzamide, HG-10-102-01, GNE-9605, JH-II-127, CZC-25146, LRRK2 inhibitor 1, DNL201, DNL151, EB-42486,

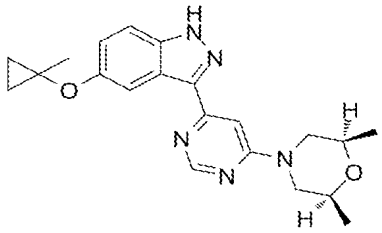
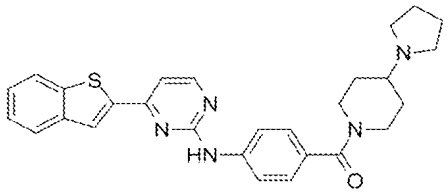
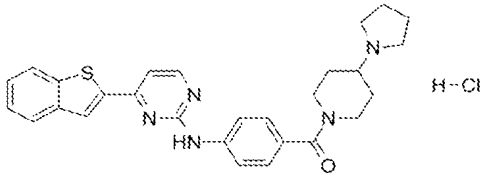
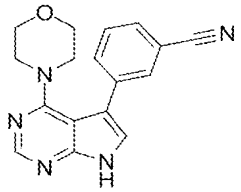
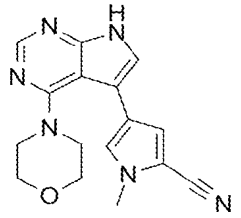
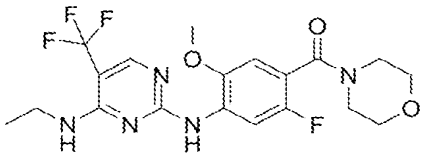
G2019S-LRRK2 inhibitor 38, G2019S-LRRK2 inhibitor 22, LRRK2 inhibitor 18, LRRK2-IN-3, LRRK2-IN-2, LRRK2-IN-4, XL01126, or PF-06456384, or a pharmaceutically acceptable salt thereof. In certain embodiments, the LRRK2 inhibitor is Compound 1, MLi-2, IKK 16, IKK 16 hydrochloride, PF-06447475, PFE-360, GNE-7915, GNE-7915 tosylate, CZC-54252, CZC-54252 hydrochloride, GNE0877, LRRK2-IN-1, TAE684, G1023, BMPPB-32, PF-06371900, sunitinib, Nov-LRRK2-11, *N*-(2-methoxyethyl)-3-(phenylsulfonamido)benzamide, HG-10-102-01, GNE-9605, JH-II-127, CZC-25146, CZC-25146 hydrochloride, LRRK2 inhibitor 1, DNL201, DNL151, EB-42486, G2019S-LRRK2 inhibitor 38, G2019S-LRRK2 inhibitor 22, LRRK2 inhibitor 18, LRRK2-IN-3, LRRK2-IN-2, LRRK2-IN-4, XL01126, or PF-06456384. Such LRRK2 inhibitors are available from the literature or commercial sources, such as from MedChemExpress USA, AdooQ Bioscience, and MedKoo Biosciences, Inc.

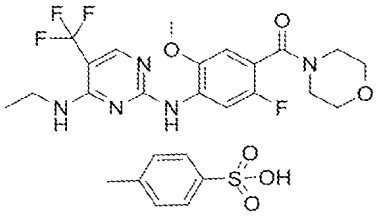
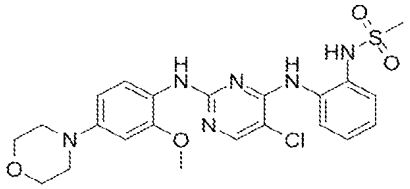
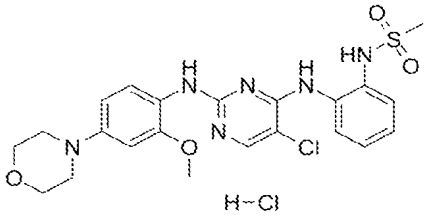
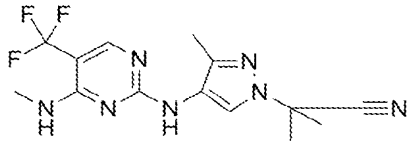
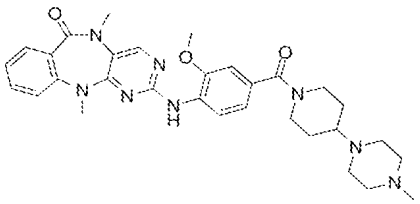
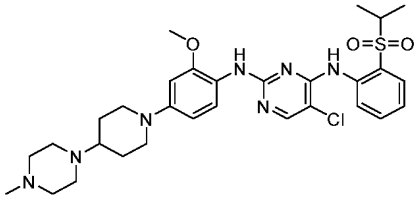
[0065] In certain embodiments, the LRRK2 inhibitor is Compound 1, MLi-2, IKK 16, PF-06447475, PFE-360, GNE-7915, CZC-54252, GNE0877, LRRK2-IN-1, TAE684, G1023, BMPPB-32, PF-06371900, sunitinib, Nov-LRRK2-11, *N*-(2-methoxyethyl)-3-(phenylsulfonamido)benzamide, HG-10-102-01, GNE-9605, JH-II-127, CZC-25146, LRRK2 inhibitor 1, DNL201, or DNL151, or a pharmaceutically acceptable salt thereof. In certain embodiments, the LRRK2 inhibitor is Compound 1, MLi-2, IKK 16, IKK 16 hydrochloride, PF-06447475, PFE-360, GNE-7915, GNE-7915 tosylate, CZC-54252, CZC-54252 hydrochloride, GNE0877, LRRK2-IN-1, TAE684, G1023, BMPPB-32, PF-06371900, sunitinib, Nov-LRRK2-11, *N*-(2-methoxyethyl)-3-(phenylsulfonamido)benzamide, HG-10-102-01, GNE-9605, JH-II-127, CZC-25146, CZC-25146 hydrochloride, LRRK2 inhibitor 1, DNL201, or DNL151. Such LRRK2 inhibitors are available from the literature or commercial sources, such as from MedChemExpress USA, AdooQ Bioscience, and MedKoo Biosciences, Inc.

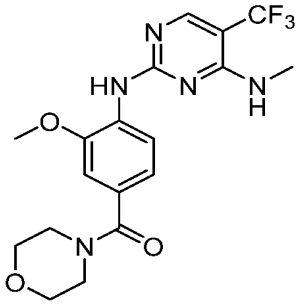
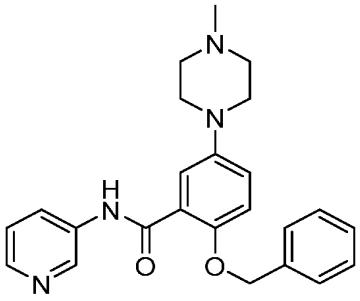
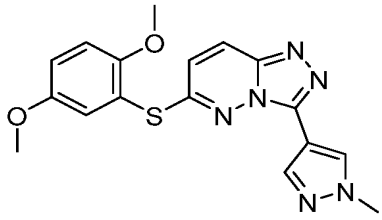
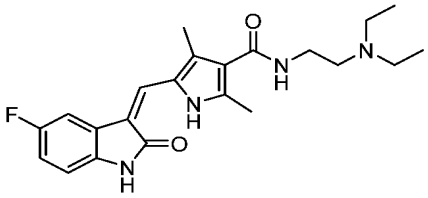
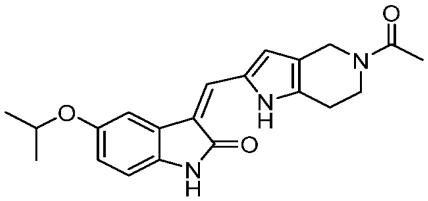
[0066] In some embodiments, the LRRK2 inhibitor is selected from the compounds in Table 1, or a pharmaceutically acceptable salt thereof.

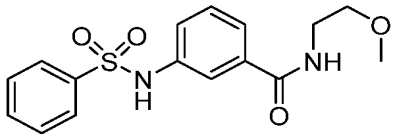
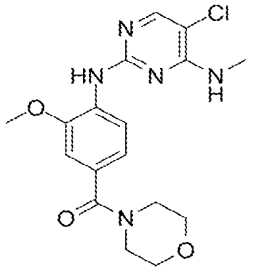
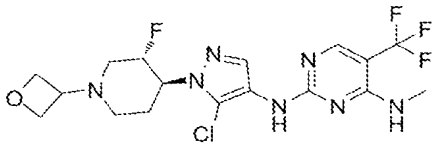
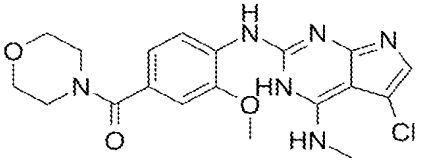
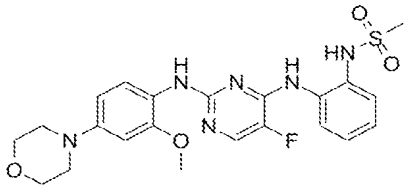
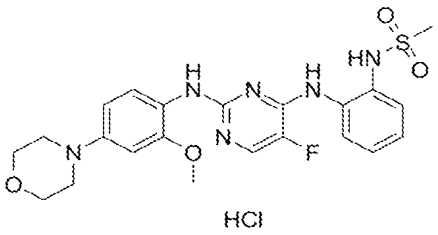
Table 1. LRRK Inhibitors

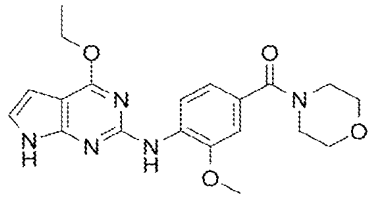
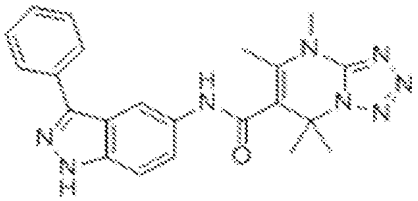
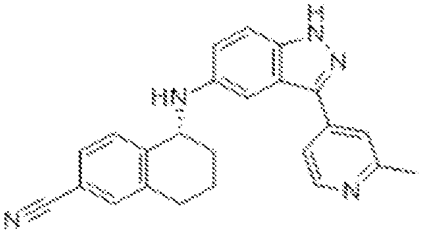
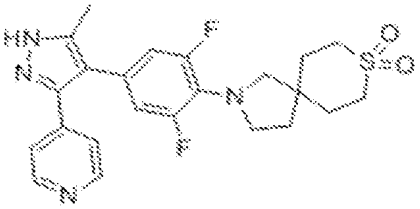
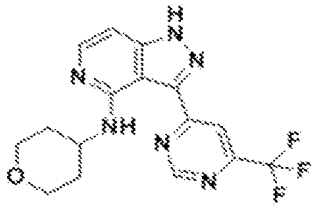
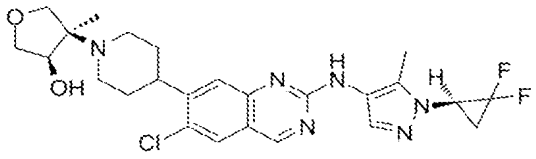
Compound Name	**Structure**	**LRRK2 Inhibition IC_{50}**	**Synthetic Reference**
Compound 1		10 nM (against both wild-type LRRK2 and the G2019S variant)	WO 2011/038572

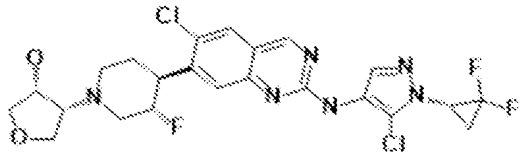
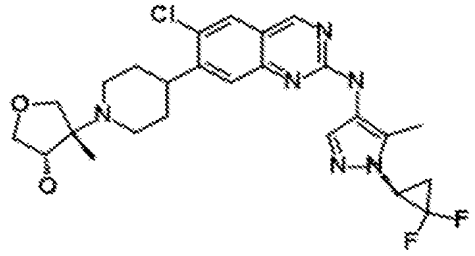
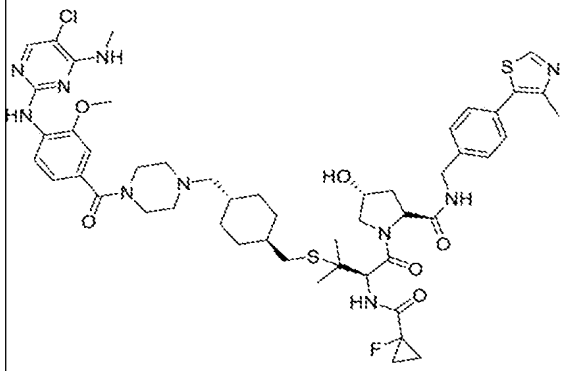
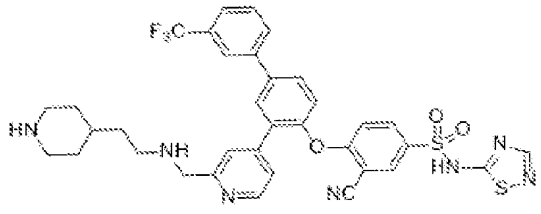
Compound Name	Structure	LRRK2 Inhibition IC_{50}	Synthetic Reference
MLi-2		0.76 nM	WO 2014/137723
IKK 16		50 nM	Waelchli et al. Bioorg Med Chem Lett. 2006 Jan 1;16(1):108-112.
IKK 16 hydrochloride		50 nM	Waelchli et al. Bioorg Med Chem Lett. 2006 Jan 1;16(1):108-112.
PF-06447475		3 nM	WO 2014/001973
PFE-360 (PF-06685360)		2.3 nM	WO 2014/001973
GNE-7915		9 nM	WO 2011/151360

Compound Name	Structure	LRRK2 Inhibition IC_{50}	Synthetic Reference
GNE-7915 tosylate		9 nM	WO 2011/151360
CZC-54252		1.28 nM (wild-type LRRK2), 1.85 nM (G2019S variant LRRK2)	WO 2009/127642
CZC-54252 hydrochloride		1.28 nM (wild-type LRRK2), 1.85 nM (G2019S variant LRRK2)	WO 2009/127642
GNE0877		3 nM	WO 2012/062783
LRRK2-IN-1		13 nM (wild-type LRRK2), 6 nM (G2019S variant LRRK2)	US 2016/0122357
TAE684		6 nM (G2019S variant LRRK2)	WO 2005/016894

Compound Name	Structure	LRRK2 Inhibition IC_{50}	Synthetic Reference
G1023		2 nM (G2019S variant LRRK2)	WO 2011/151360
BMPPB-32		6 nM (G2019S variant LRRK2)	WO 2011/038572
PF-06371900		64 nM (G2019S variant LRRK2)	WO 2013/166276
Sunitinib		19 nM	US 2002/0156292
Nov-LRRK2-11		4 nM	Troxler, et al. Bioorg. Med. Chem. Lett. 2013, 23(14): 4085-4090.

Compound Name	Structure	LRRK2 Inhibition IC_{50}	Synthetic Reference
N-(2-methoxyethyl)-3-(phenylsulfonamido)benzamide			Li, et al. Hum. Mol. Genet. 2014, 23(23): 6212-6222.
HG-10-102-01		23.3 nM (wild-type LRRK2), 3.2 nM (G2019S variant LRRK2)	WO 2011/151360
GNE-9605		19 nM	WO 2012/062783
JH-II-127		6.6 nM (wild-type LRRK2), 2.2 nM, (G2019S variant LRRK2), 47.7 nM (A2016T variant LRRK2)	WO 2016/130920
CZC-25146		4.76 nM (wild-type LRRK2), 6.87 nM (G2019S variant LRRK2)	WO 2009/127642
CZC-25146 hydrochloride		4.76 nM (wild-type LRRK2), 6.87 nM (G2019S variant LRRK2)	WO 2009/127642

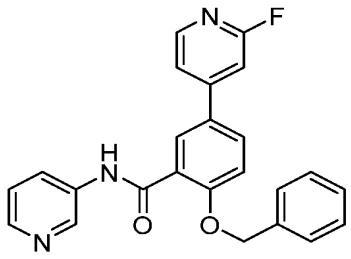
Compound Name	Structure	LRRK2 Inhibition IC_{50}	Synthetic Reference
LRRK2 inhibitor 1		pIC_{50} = 6.8.	WO 2015/113451
EB-42486		<0.2 nM	Garofalo, et al. J Med Chem. 2020 Dec 10;63(23):14821-14839.
G2019S-LRRK2 inhibitor 38		<1 nM (G2019S-LRRK2)	Leśniak, et al. Eur J Med Chem. 2022 Feb 5;229:114080.
G2019S-LRRK2 inhibitor 22		4.6 nM (G2019S-LRRK2)	Leśniak RK, et al. Eur J Med Chem. 2022 Aug 24;242:114693.
LRRK2 inhibitor 18		Ki of 4.1 nM	WO2013139882
LRRK2-IN-3			WO2021080929

Compound Name	Structure	LRRK2 Inhibition IC_{50}	Synthetic Reference
LRRK2-IN-2		<0.6 nM	WO2021080929
LRRK2-IN-4			
XL01126			Xingui, et al ChemRxiv (2022), 1-27
PF-06456384		3 nM and 11 nM for WT LRRK and G2019S LRRK2, respectively	WO2015181797

Compound 1 and Compositions Thereof

[0067] In one embodiment, the LRRK2 inhibitor is Compound 1. Compound 1 is described in U.S. Pat. Nos 8,778,939 and 10,058,559, and published WIPO applications WO 2016/007540 and WO

2019/221566. The chemical name of Compound 1 is 2-(benzyloxy)-5-(2-fluoropyridin-4-yl)-N-(pyridin-3-yl)benzamide, and the compound has the following structure:



1.

[0068] The synthesis of Compound 1 is known in the art. Compound 1 is also commercially available (Tocris Biosciences, product no. 4629).

LRRK2 Inhibitors and Pharmaceutical Compositions

[0069] Also provided herein, in some embodiments, are pharmaceutical compositions that comprise compounds as described herein, and one or more pharmaceutically acceptable vehicles selected from carriers, adjuvants, and excipients.

[0070] Suitable pharmaceutically acceptable vehicles may include, for example, inert solid diluents and fillers, diluents, including sterile aqueous solution and various organic solvents, permeation enhancers, solubilizers, and adjuvants. Such compositions are prepared in a manner well known in the pharmaceutical art. *See, e.g.*, Remington's Pharmaceutical Sciences, Mace Publishing Co., Philadelphia, Pa. 17th Ed. (1985); and Modern Pharmaceutics, Marcel Dekker, Inc. 3rd Ed. (G.S. Banker & C.T. Rhodes, Eds.).

[0071] The pharmaceutical compositions may be administered in either single or multiple doses. The pharmaceutical composition may be administered by various methods including, for example, rectal, buccal, intranasal, and transdermal routes. In certain embodiments, the pharmaceutical composition may be administered by intra-arterial injection, intravenously, intraperitoneally, parenterally, intramuscularly, subcutaneously, orally, topically, or as an inhalant.

[0072] One mode for administration is parenteral, for example, by injection. The forms in which the pharmaceutical compositions described herein may be incorporated for administration by injection include, for example, aqueous or oil suspensions, or emulsions, with sesame oil, corn oil, cottonseed oil, or peanut oil, as well as elixirs, mannitol, dextrose, or a sterile aqueous solution, and similar pharmaceutical vehicles.

[0073] Oral administration may be another route for administration of the compounds described herein. Administration may be via, for example, capsule or enteric coated tablets. In making the pharmaceutical compositions that include at least one compound described herein, the active ingredient is usually diluted by an excipient and/or enclosed within such a carrier that can be in the form of a capsule,

sachet, paper or other container. When the excipient serves as a diluent, it can be in the form of a solid, semi-solid, or liquid material, which acts as a vehicle, carrier or medium for the active ingredient. Thus, the compositions can be in the form of tablets, pills, powders, lozenges, sachets, cachets, elixirs, suspensions, emulsions, solutions, syrups, aerosols (as a solid or in a liquid medium), ointments containing, for example, up to 10% by weight of the active compound, soft and hard gelatin capsules, sterile injectable solutions, and sterile packaged powders.

[0074] Some examples of suitable excipients include lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate, alginates, tragacanth, gelatin, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidone, cellulose, sterile water, syrup, and methyl cellulose. The formulations can additionally include lubricating agents such as talc, magnesium stearate, and mineral oil; wetting agents; emulsifying and suspending agents; preserving agents such as methyl and propylhydroxy-benzoates; sweetening agents; and flavoring agents.

[0075] The compositions that include at least one compound described herein can be formulated so as to provide quick, sustained or delayed release of the active ingredient after administration to the subject by employing procedures known in the art. Controlled release drug delivery systems for oral administration include osmotic pump systems and dissolutional systems containing polymer-coated reservoirs or drug-polymer matrix formulations. Examples of controlled release systems are given in U.S. Patent Nos. 3,845,770; 4,326,525; 4,902,514; and 5,616,345. Another formulation for use in the methods disclosed herein employ transdermal delivery devices ("patches"). Such transdermal patches may be used to provide continuous or discontinuous infusion of the compounds described herein in controlled amounts. The construction and use of transdermal patches for the delivery of pharmaceutical agents is well known in the art. *See, e.g.*, U.S. Patent Nos. 5,023,252, 4,992,445, and 5,001,139. Such patches may be constructed for continuous, pulsatile, or on demand delivery of pharmaceutical agents.

[0076] For preparing solid compositions such as tablets, the principal active ingredient may be mixed with a pharmaceutical excipient to form a solid preformulation composition containing a homogeneous mixture of a compound described herein. When referring to these preformulation compositions as homogeneous, the active ingredient may be dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills, and capsules.

[0077] The tablets or pills of the compounds described herein may be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action, or to protect from the acid conditions of the stomach. For example, the tablet or pill can include an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer that serves to resist disintegration in the stomach and permit the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be

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

[0078] Compositions for inhalation or insufflation may include solutions and suspensions in pharmaceutically acceptable, aqueous or organic solvents, or mixtures thereof, and powders. The liquid or solid compositions may contain suitable pharmaceutically acceptable excipients as described herein. In some embodiments, the compositions are administered by the oral or nasal respiratory route for local or systemic effect. In other embodiments, compositions in pharmaceutically acceptable solvents may be nebulized by use of inert gases. Nebulized solutions may be inhaled directly from the nebulizing device or the nebulizing device may be attached to a facemask tent, or intermittent positive pressure breathing machine. Solution, suspension, or powder compositions may be administered, preferably orally or nasally, from devices that deliver the formulation in an appropriate manner.

[0079] In some embodiments, the therapeutically effective amount of the leucine-rich repeat kinase 2 inhibitor is administered once daily. In some embodiments, the therapeutically effective amount of the leucine-rich repeat kinase 2 inhibitor is administered over two doses in a day.

[0080] In some embodiments, the therapeutically effective amount of the leucine-rich repeat kinase 2 inhibitor is formulated for oral administration. In some embodiments, the therapeutically effective amount of the leucine-rich repeat kinase 2 inhibitor is in tablet form or capsule form.

[0081] In some embodiments, the therapeutically effective amount of the leucine-rich repeat kinase 2 inhibitor is formulated for parenteral administration.

[0082] In some embodiments, the therapeutically effective amount of the leucine-rich repeat kinase 2 inhibitor is formulated for inhalation.

[0083] In some embodiments, the leucine-rich repeat kinase 2 inhibitor is Compound 1 or a pharmaceutically acceptable salt thereof.

[0084] In some embodiments, the therapeutically effective amount of Compound 1 is about 1 mg/kg to about 500 mg/kg. In some embodiments, the therapeutically effective amount of Compound 1 is about 25 mg/kg to about 400 mg/kg. In some embodiments, the therapeutically effective amount of Compound 1 is about 50 mg/kg to about 300 mg/kg. In some embodiments, the therapeutically effective amount of Compound 1 is about 75 mg/kg to about 200 mg/kg. In some embodiments, the therapeutically effective amount of Compound 1 is about 100 mg/kg to about 150 mg/kg.

[0085] In some embodiments, the therapeutically effective amount of Compound 1 is about 1 mg/kg. In some embodiments, the therapeutically effective amount of Compound 1 is about 25 mg/kg. In some embodiments, the therapeutically effective amount of Compound 1 is about 50 mg/kg. In some embodiments, the therapeutically effective amount of Compound 1 is about 75 mg/kg. In some embodiments, the therapeutically effective amount of Compound 1 is about 100 mg/kg. In some embodiments, the therapeutically effective amount of Compound 1 is about 150 mg/kg. In some

embodiments, the therapeutically effective amount of Compound 1 is about 200 mg/kg. In some embodiments, the therapeutically effective amount of Compound 1 is about 300 mg/kg. In some embodiments, the therapeutically effective amount of Compound 1 is about 400 mg/kg. In some embodiments, the therapeutically effective amount of Compound 1 is about 500 mg/kg.

Combination Therapy

[0086] In some embodiments, methods provided herein further comprise administering one or more of an additional therapeutic agent. In some embodiments, the additional therapeutic agent is an anti-inflammatory agent.

[0087] In some embodiments, the anti-inflammatory agent is a corticosteroid, such as beclomethasone, betamethasone, budesonide, clobetasol, flunisolide, fluocinolone, fluocinonide, fluticasone, halobetasol, hydrocortisone, methylprednisone, mometasone, prednisolone, prednisone, and triamcinolone. In some embodiments, the anti-inflammatory agent is a non-steroidal anti-inflammatory (NSAIDs), such as a non-selective COX inhibitor or a selective COX-2 inhibitor. Non-selective COX inhibitors include, but are not limited to, salicylic acid derivates (e.g., aspirin, sodium salicylates, choline magnesium trisalicylate, salsalate, diflunisal, sulfasalazine, mesalamine, and olsalazine), para-aminophenol derivatives (e.g., acetaminophen), indole and indene acetic acids (e.g., tolmetin, diclofenac, and ketorolac), heteroaryl acetic acids (e.g., flurbiprofen, ketoprofen, fenprofen, ibuprofen, naproxen, and oxaprozin), anthranilic acids or fenamates (e.g., mefenamic acid and meclofenamic acid), enolic acids (e.g., piroxicam and meloxicam), and alkanones (e.g., nabumetone). Selective COX-2 inhibitors include, but are not limited to, diaryl-substituted pyrazoles (e.g., celecoxib), indole acetic acids (e.g., etodolac), and sulfonanilides (e.g., nimesulide).

[0088] In some embodiments, the additional therapeutic agent is an immunosuppressive agent. Non-limiting examples of immunosuppressive agents include methotrexate, cyclophosphamide, mizoribine, chlorambucil, cyclosporine, tacrolimus, mycophenolate mofetil, azathioprine, sirolimus, voclosporin, deoxyspergualin, leflunomide, and its malononitriloamide analogs.

[0089] It is understood that modifications which do not substantially affect the activity of the various embodiments of this disclosure are also included within the definition of the disclosure provided herein. Accordingly, the following examples are intended to illustrate but not limit the present disclosure.

EXAMPLES

Example 1: MRL Murine Model Study

[0090] Female MRL/MpJ-Fas^{lpr}/J mice, a well-accepted standard for the study of human SLE, due to a mutation that leads to the spontaneous development of an autoimmune disease, presenting with hyperactive, self-reactive B and T cells, autoantibodies directed against nuclear antigens, and defective clearance of immune complexes leading to fatal immune glomerulonephritis, were separated into test

groups (group size, n=10). Test agents were administered before presentation of disease symptoms, at a test subject age of 8-9 weeks. Compound 1 was dosed orally at 30 mg/kg. The reference group received cyclophosphamide via intraperitoneal injection, dosed at 50 mg/kg. During the in-life phase of the study, the Compound 1 test group was compared to a negative control group (vehicle only) and a positive control group (cyclophosphamide treatment), using multiple efficacy measures assessing the health of test subjects' lymph nodes and kidneys. Lymphadenopathy, skin lesion, and proteinuria scoring parameters are presented in Table 2.

Table 2: In-Life Scoring Parameters

Test	In-Life Scoring Parameters
Lymphadenopathy	**0** = None **1** = Small (<1 cm diameter combined) at one bilateral site. **2** = Small at two bilateral sites. **3** = Small at three bilateral sites. **4** = Large (>1 cm combined) at one bilateral site and small at two.
Skin Lesions	**0** = None **1** = 1 or 2 small (2-4 mm in length). **2** = Lesion(s) larger than a "1", but with total area <0.5 cm^2. **3** = Lesion(s) with total area >0.5, but <1.0 cm^2.
Proteinuria	**0** = None **1** = 1–29 mg/dL **2** = 30–99 mg/dL **3** = 100–299 mg/dL **4** = 300–1999 mg/dL **5** = ≥2000 mg/dL

[0091] On day 61, the test groups were euthanized, and lymph node weight and kidney histology scores were compared for the Compound 1 test group, the negative control group, and the positive control group. Samples were graded for severity, with histological scoring parameters for tubule basophilia, tubule dilation, glomerulonephritis, chronic interstitial inflammation, and chronic papillary inflammation presented in Table 3.

Table 3: Histological Scoring Parameters

Test	Histological Scoring Parameters
- Tubule Basophilia - Tubule Dilation -Glomerulonephritis - Chronic Interstitial Inflammation - Chronic Papillary Inflammation	**0** = Absent **1** = Minimal **2** = Mild **3** = Moderate **4** = Marked **5** = Severe

[0092] Mice treated with Compound 1 exhibited a decrease in lymphadenopathy score, a measure of the size and characteristics of the lymph nodes in the subjects, as compared to the negative control group at days 42, 48, and 56 (**FIG. 1**). Similarly, upon sacrifice of the test groups at completion of the study, the group treated with Compound 1 exhibited reduced inguinal lymph node weight, but it was not statistically significant ($p = 0.06$) when compared to samples collected from subjects treated with only vehicle (**FIG. 3**). Swelling of lymph nodes is a common manifestation in SLE.

[0093] The appearance and severity of skin lesions present in the group treated with Compound 1 was significantly lower (p value = < 0.0001) than those present in the negative control group, and comparable to the test group being treated with cyclophosphamide (**FIG. 2**), indicating a decrease in inflammation and immune response when compared with the untreated test group.

[0094] Proteinuria is a standard clinical measure of renal function, with healthy kidneys filtering little protein from blood for excretion. The damage present in kidneys from the immune response and inflammation associated with SLE can be observed by tracking protein concentration in test subject urine. The test group treated with Compound 1 displayed a non-statistical decrease in urine protein content when compared to that seen in the negative control group, treated with only vehicle (**FIG. 4**).

[0095] Similarly, the presence of urea in blood is also indicative of ineffective filtering and poor renal function. The test group treated with Compound 1 showed a comparable decrease ($p = < 0.05$) in blood urea content as was observed in the group treated with cyclophosphamide, with both having blood urea concentrations notably lower than that observed in the negative control group (**FIG. 5**).

[0096] Anti-double stranded DNA antibodies form during the autoimmune response to extracellular DNA in patients with SLE, leading to inflammation and subsequent kidney and skin damage. The test group treated with Compound 1 displayed comparable levels of anti-dsDNA antibodies to those treated with only vehicle. The cyclophosphamide treated group showed a non-statistically significant reduction in anti-dsDNA antibodies (**FIG. 6**).

[0097] Kidney samples were collected from the sacrificed test groups for histological analysis. Mice treated with Compound 1 showed a statistically significant decrease ($p = 0.01$-0.05) in tubule basophilia histology scores (**FIG. 7**), and a reduction ($p = 0.1$) in tubule dilation/casts histology scores (**FIG. 8**), when compared to those administered only vehicle, indicating a decrease in observed renal inflammation and damage.

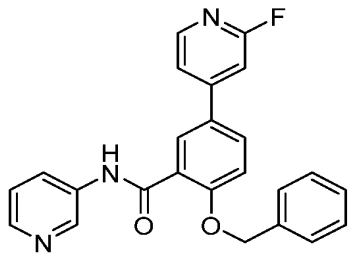
[0098] Similarly, histological analysis of kidney tissue from the test groups for glomerulonephritis, inflammation of the kidney's filter structures, showed a reduction ($p = 0.1$) in inflammation for the test group treated with Compound 1, when compared to the test group administered only vehicle (**FIG. 9**).

[0099] Further, kidney tissue samples from mice treated with Compound 1 exhibited a statistically significant reduction ($p = 0.01$-0.05) in histology scoring for chronic interstitial inflammation (**FIG. 10**), a reduction in histology scoring for chronic papillary inflammation (**FIG. 11**), and an overall statistically significant reduction ($p = < 0.01$-0.05) in the summation of histology scores (**FIG. 12**), when compared to the test group administered only vehicle, indicating a decrease in observed renal damage.

[00100] Although the disclosure has been described with reference to the disclosed embodiments, those skilled in the art will readily appreciate that the specific examples and studies detailed above are only illustrative. It should be understood that various modifications can be made without departing from the spirit of the disclosure.

WHAT IS CLAIMED:

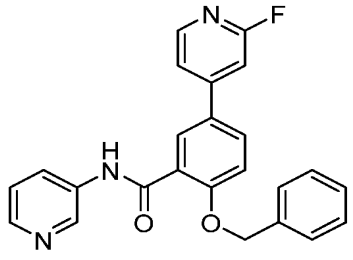
1. A method for treating systemic lupus erythematosus (SLE), comprising administering to a patient in need thereof, a therapeutically effective amount of Compound 1:



1,

or a pharmaceutically acceptable salt thereof.

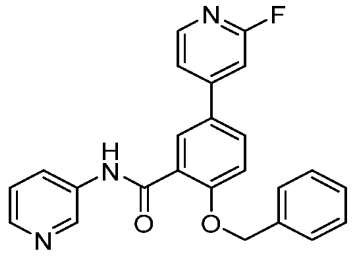
2. A method for improving kidney function, comprising administering to a patient in need thereof, a therapeutically effective amount of Compound 1:



1,

or a pharmaceutically acceptable salt thereof.

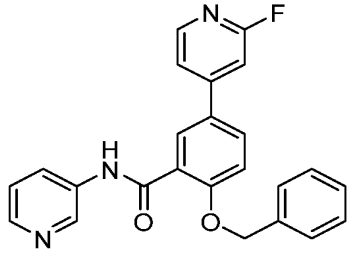
3. A method for inhibiting the production of double-stranded DNA antibody (anti-dsDNA antibody), comprising administering to a patient in need thereof, a therapeutically effective amount of Compound 1:



1,

or a pharmaceutically acceptable salt thereof.

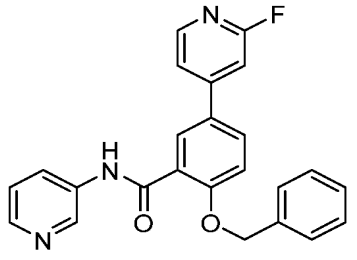
4. A method for decreasing the concentration of blood urea nitrogen (BUN), comprising administering to a patient in need thereof, a therapeutically effective amount of Compound 1:



1,

or a pharmaceutically acceptable salt thereof.

5. A method for decreasing proteinuria, comprising administering to a patient in need thereof, a therapeutically effective amount of Compound 1:



1,

or a pharmaceutically acceptable salt thereof.

6. The method of any preceding claim, wherein the treating comprises inhibiting, lessening, or delaying the onset or progression of, fatigue, fever, joint pain, joint stiffness, joint swelling, rashes, skin lesions, shortness of breath, chest pain, dry eyes, headaches, confusion, memory loss, sun sensitivity, oral ulcers, arthritis, lung damage, heart problems, kidney damage, lupus nephritis, lymphadenopathy, seizures, psychosis, blood cell abnormalities, or immunological abnormalities.

7. The method of any preceding claim, wherein the treating comprises inhibiting, lessening, or delaying the onset or progression of, skin lesions, lymphadenopathy, kidney damage, lupus nephritis, or inflammation.

8. The method of any preceding claim, wherein the patient is experiencing a lupus flare.

9. The method of any preceding claim, wherein the compound, or pharmaceutically acceptable salt thereof, is administered in a pharmaceutical composition.

10. The method of claim 9, wherein the pharmaceutical composition is formulated for oral administration.

11. The method of claim 10, wherein the pharmaceutical composition is in tablet form or capsule form.

12. The method of any one of claims 9-11, wherein the pharmaceutical composition is administered once daily.

13. The method of any preceding claim, wherein the patient also suffers from another autoimmune condition.

14. The method of claim 13, wherein the autoimmune condition is Sjogren's syndrome, antiphospholipid syndrome, thyroiditis, hemolytic anemia, or idiopathic thrombocytopenia purpura.

15. The method of any preceding claim, further comprising administering an additional therapeutic agent.

16. The method of claim 15, wherein the additional therapeutic agent is selected from the group consisting of a nonsteroidal anti-inflammatory drug (NSAID), an antimalarial drug, a corticosteroid, an immunosuppressant, and a biologic.

17. The method of claim 15, wherein the additional therapeutic agent is naproxen sodium, ibuprofen, hydroxychloroquine, prednisone, methylprednisolone, azathioprine (Imuran, Azasan), mycophenolate (Cellcept), methotrexate (Trexall, Xatmep, others), cyclosporine (Sandimmune, Neoral, Gengraf), leflunomide (Arava), belimumab (Benlysta), voclosporin (Lupkynis), or rituximab.

ABSTRACT

Provided is a method for treating systemic lupus erythematosus (SLE) in a patient in need thereof comprising administering a therapeutically effective amount of a leucine-rich repeat kinase 2 (LRRK2) inhibitor.

SMRH:4863-6985-2987.2

FIG. 1

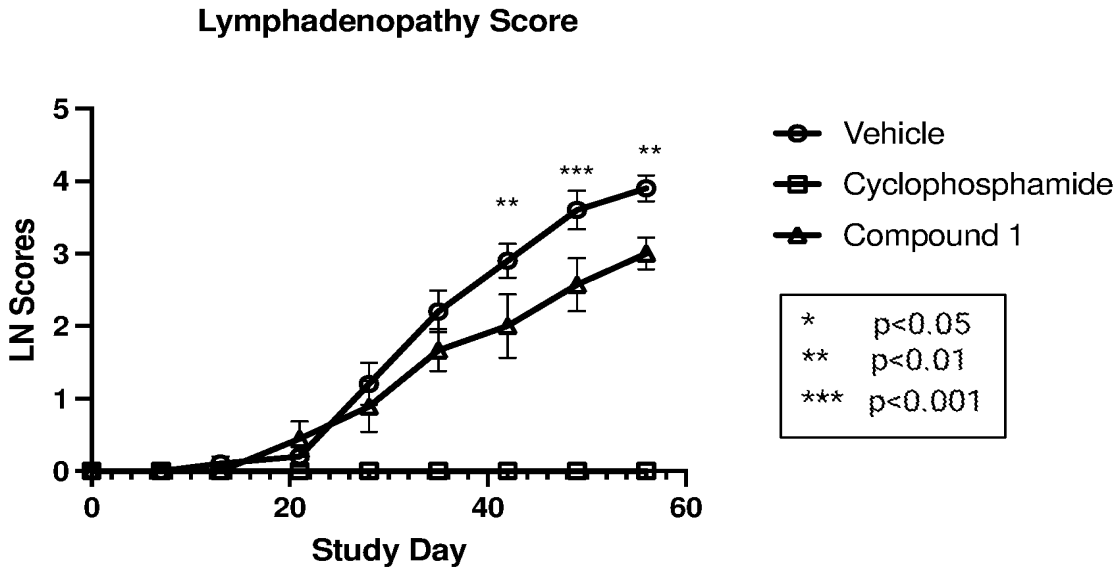

Lymphadenopathy Score
LN Scores
Study Day
0
20
40
60
1
2
3
4
5
**
***
**
Vehicle
Cyclophosphamide
Compound 1
* p<0.05
** p<0.01
*** p<0.001

FIG. 2

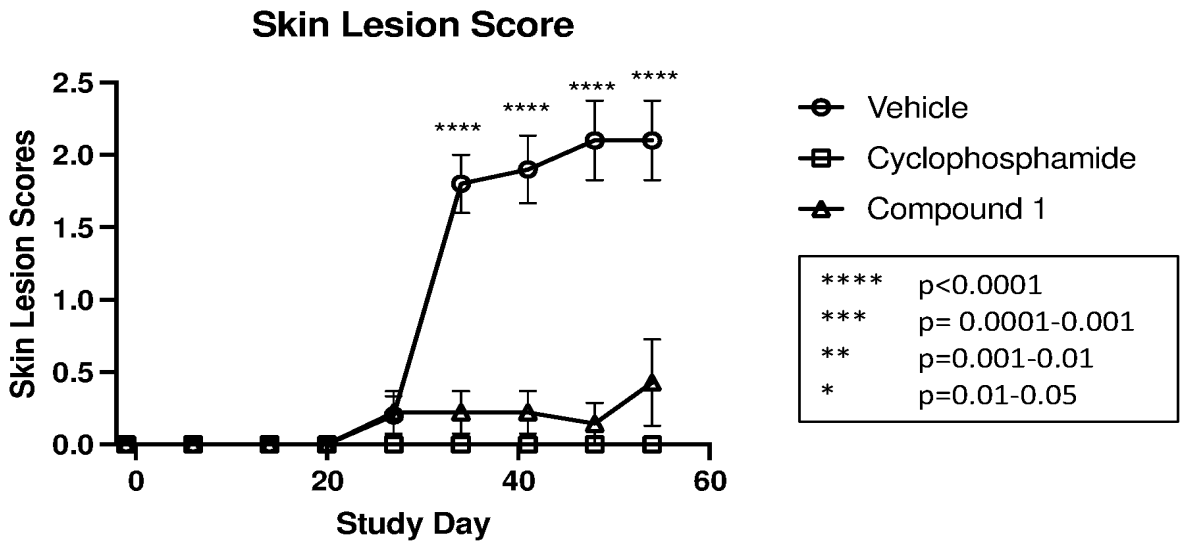

Skin Lesion Score
Skin Lesion Scores
Study Day
0
20
40
60
0.0
0.5
1.0
1.5
2.0
2.5
****
****
****
****
Vehicle
Cyclophosphamide
Compound 1
**** p<0.0001
*** p= 0.0001-0.001
** p=0.001-0.01
* p=0.01-0.05

FIG. 3

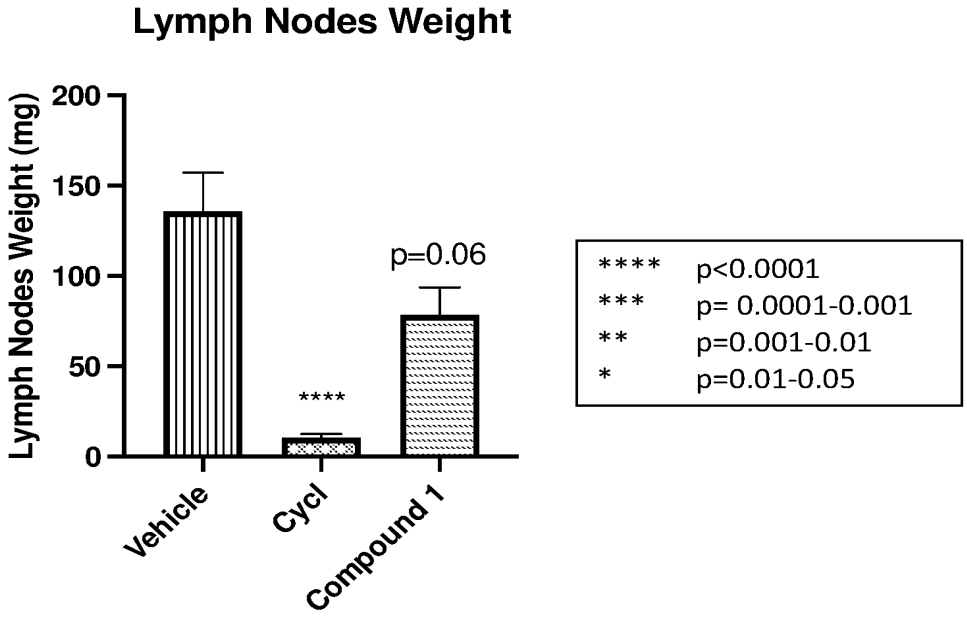

Lymph Nodes Weight
Lymph Nodes Weight (mg)
200
150
100
50
0
****
p=0.06
Vehicle
Cycl
Compound 1
**** p<0.0001
*** p= 0.0001-0.001
** p=0.001-0.01
* p=0.01-0.05

FIG. 4

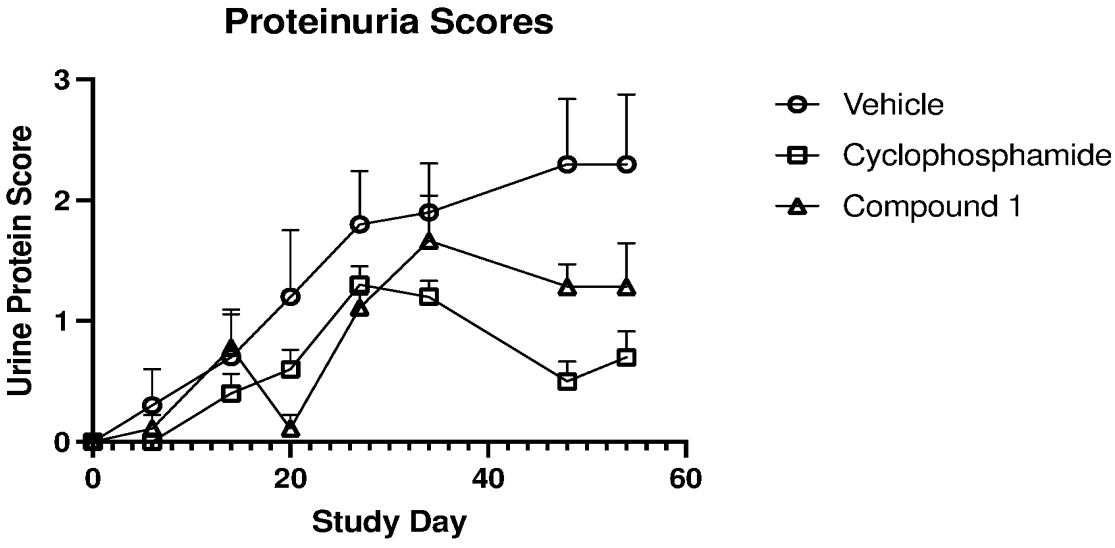

Proteinuria Scores
Urine Protein Score
3
2
1
0
0
20
40
60
Study Day
Vehicle
Cyclophosphamide
Compound 1

FIG. 5

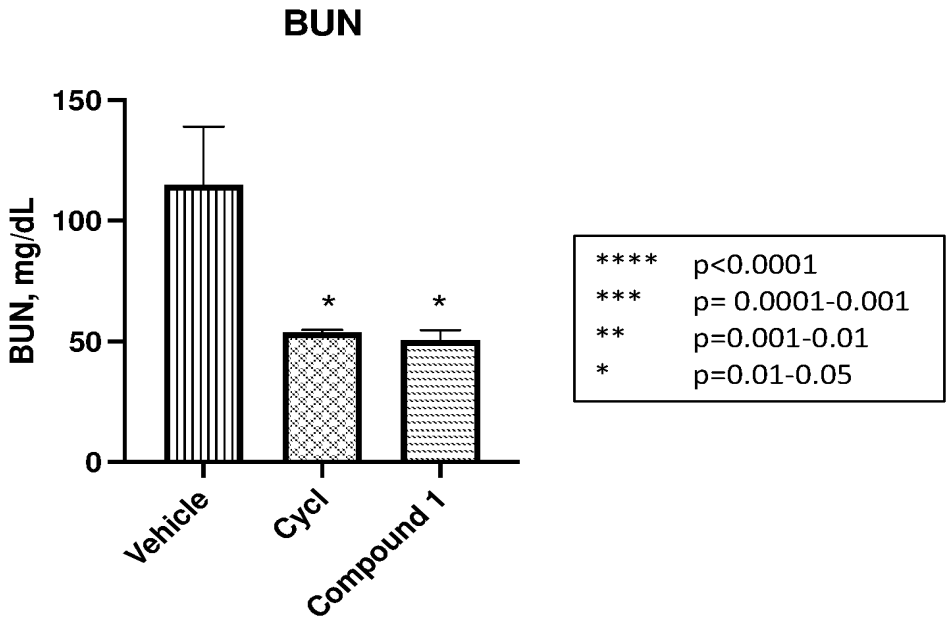

BUN
BUN, mg/dL
150
100
50
0
*
*
Vehicle
Cycl
Compound 1
**** p<0.0001
*** p= 0.0001-0.001
** p=0.001-0.01
* p=0.01-0.05

FIG. 6

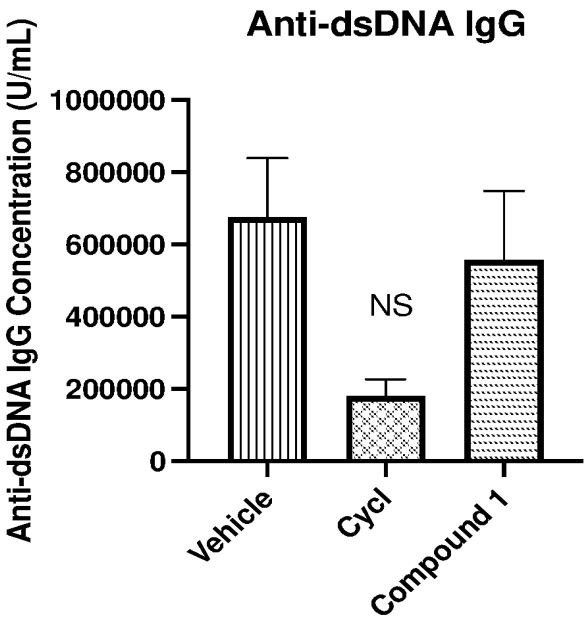

Anti-dsDNA IgG
Anti-dsDNA IgG Concentration (U/mL)
1000000
800000
600000
400000
200000
0
NS
Vehicle
Cycl
Compound 1

FIG. 7

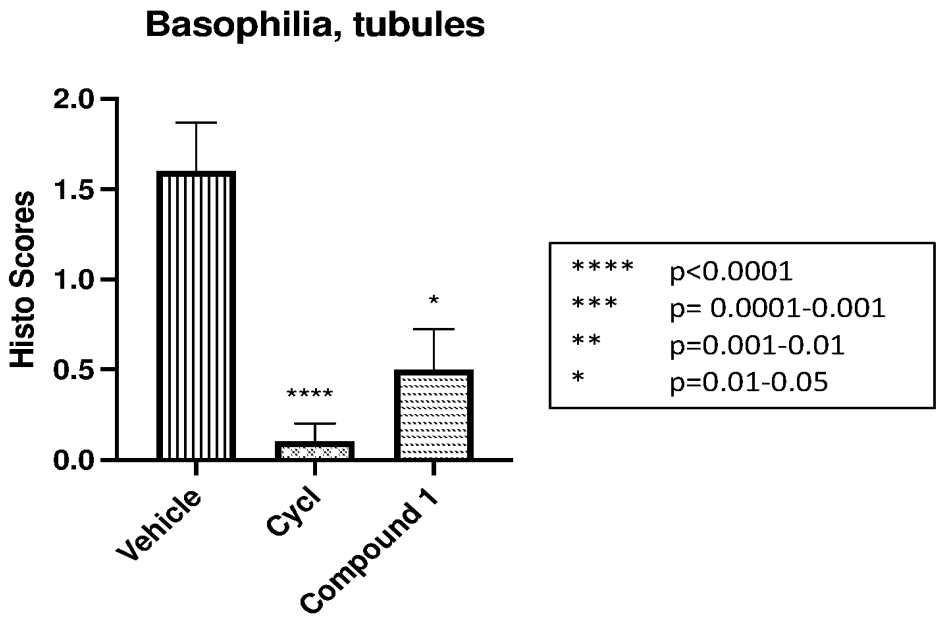

Basophilia, tubules
Histo Scores
2.0
1.5
1.0
0.5
0.0
****
*
Vehicle
Cycl
Compound 1
**** p<0.0001
*** p= 0.0001-0.001
** p=0.001-0.01
* p=0.01-0.05

FIG. 8

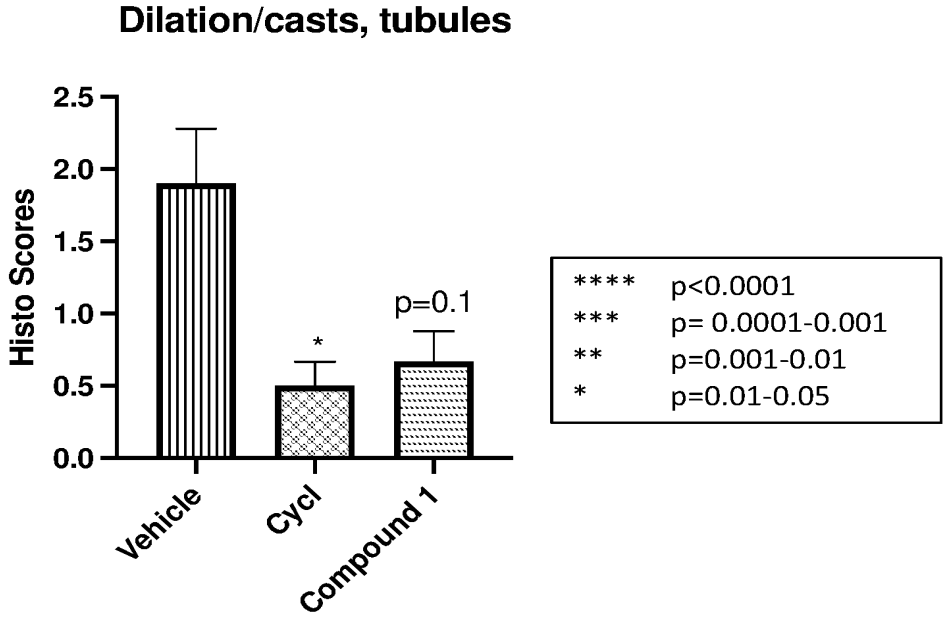

Dilation/casts, tubules
Histo Scores
2.5
2.0
1.5
1.0
0.5
0.0
*
p=0.1
Vehicle
Cycl
Compound 1
**** p<0.0001
*** p= 0.0001-0.001
** p=0.001-0.01
* p=0.01-0.05

FIG. 9

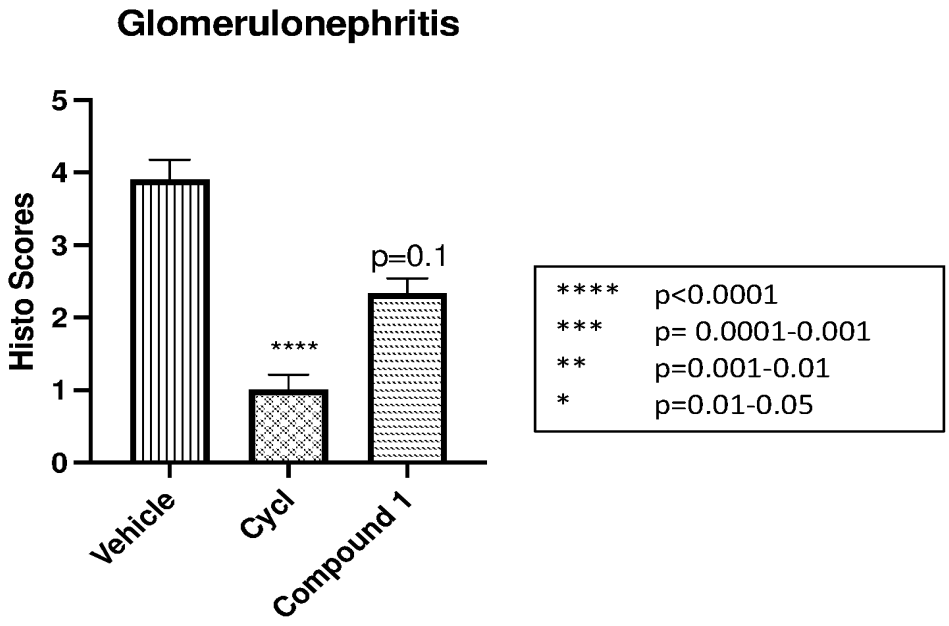

Glomerulonephritis
Histo Scores
5
4
3
2
1
0
****
p=0.1
Vehicle
Cycl
Compound 1
**** p<0.0001
*** p= 0.0001-0.001
** p=0.001-0.01
* p=0.01-0.05

FIG. 10

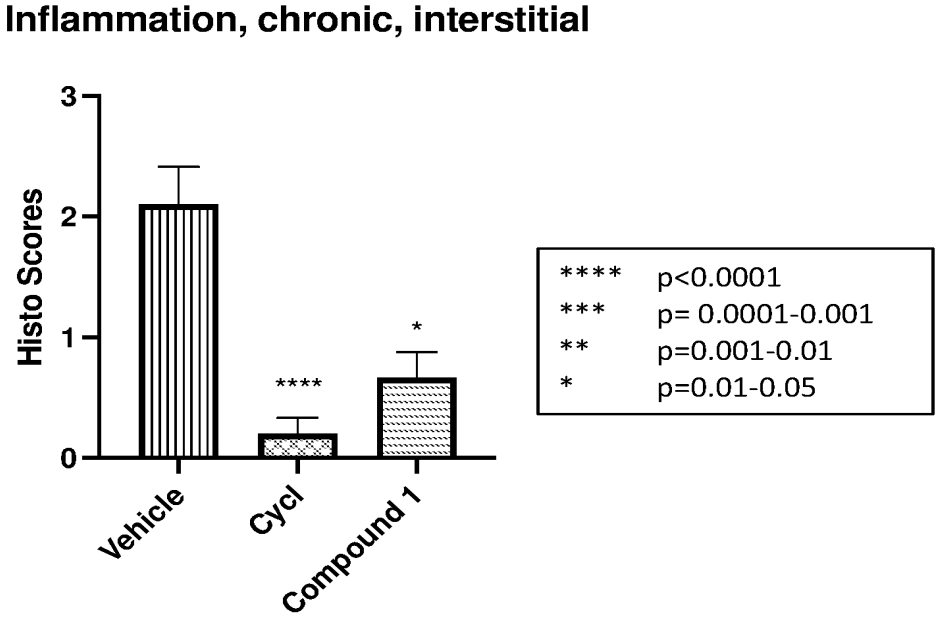

Inflammation, chronic, interstitial
Histo Scores
3
2
1
0
****
*
Vehicle
Cycl
Compound 1
**** p<0.0001
*** p= 0.0001-0.001
** p=0.001-0.01
* p=0.01-0.05

FIG. 11

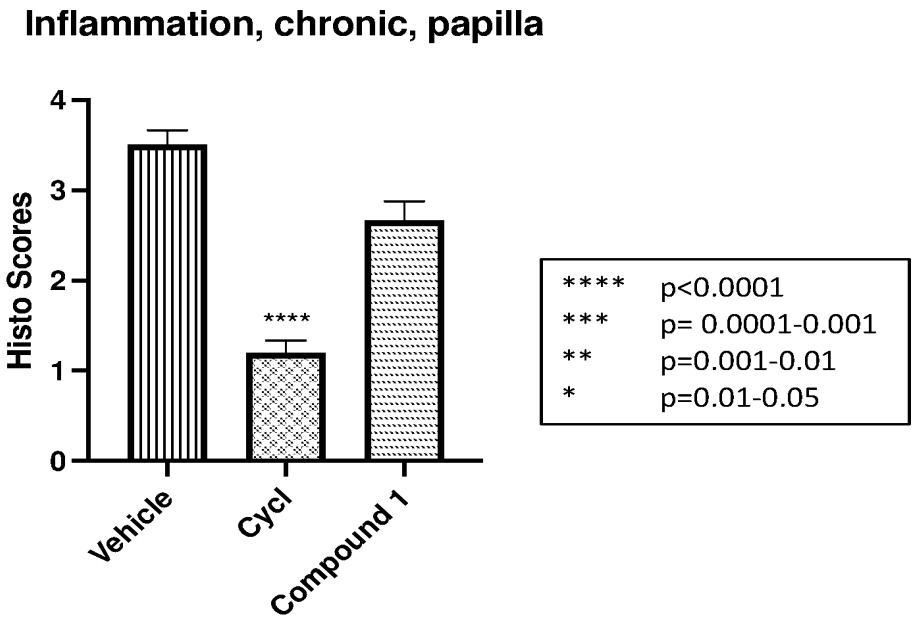
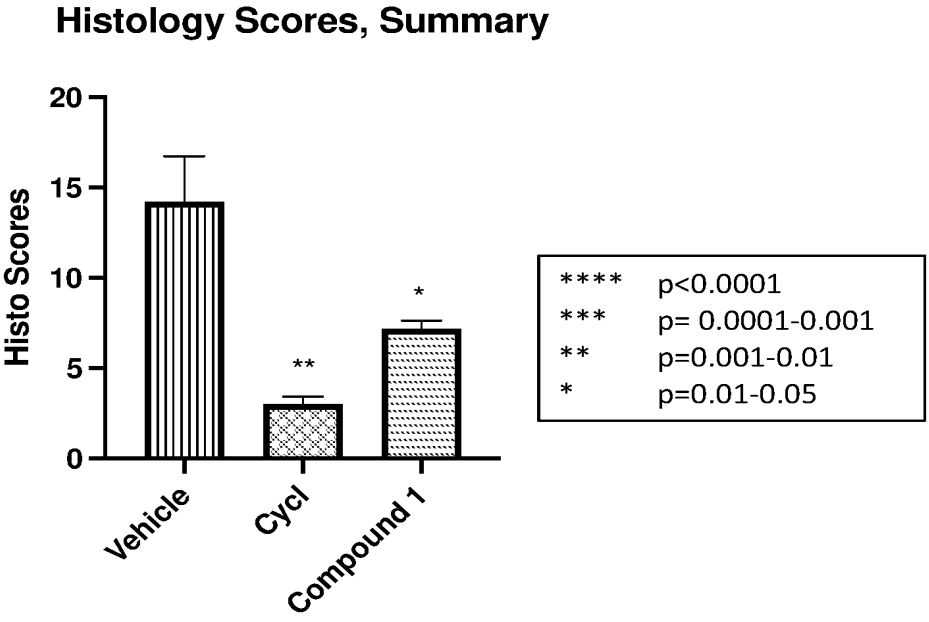

Inflammation, chronic, papilla
Histo Scores
0
1
2
3
4
****
Vehicle
Cycl
Compound 1
**** p<0.0001
*** p= 0.0001-0.001
** p=0.001-0.01
* p=0.01-0.05

FIG. 12


Histology Scores, Summary
Histo Scores
0
5
10
15
20
**
*
Vehicle
Cycl
Compound 1
**** p<0.0001
*** p= 0.0001-0.001
** p=0.001-0.01
* p=0.01-0.05

Electronic Patent Application Fee Transmittal

Application Number:	
Filing Date:	
Title of Invention:	METHODS FOR TREATING SYSTEMIC LUPUS ERYTHEMATOSUS
First Named Inventor/Applicant Name:	ARIA PHARMACEUTICALS, INC.
Filer:	Lacie C. Hirayama/Anthony Wychules
Attorney Docket Number:	72MM-341180-WO

Filed as Small Entity

Filing Fees for International Application (PCT) for filing in the US receiving office

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
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SUPPL. INTL FILING FEE (EACH PAGE > 30)	1703	9	16	144
INTERNATIONAL SEARCH (EPO)	1704	1	1816	1816
INTL FILING FIRST 30PGS EFS W/ ZIP FILE	1710	1	1221	1221
Pages:				
Claims:				
Miscellaneous-Filing:				
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Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Miscellaneous:				
		Total in USD ($)		**3311**

Electronic Acknowledgement Receipt

EFS ID:	46900502
Application Number:	
International Application Number:	PCT/US22/47908
Confirmation Number:	2252
Title of Invention:	METHODS FOR TREATING SYSTEMIC LUPUS ERYTHEMATOSUS
First Named Inventor/Applicant Name:	ARIA PHARMACEUTICALS, INC.
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Filer:	Lacie C. Hirayama/Anthony Wychules
Filer Authorized By:	Lacie C. Hirayama
Attorney Docket Number:	72MM-341180-WO
Receipt Date:	26-OCT-2022
Filing Date:	
Time Stamp:	18:13:26
Application Type:	International Application (PCT) for filing in the US receiving office
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Multipart Description/PDF files in .zip description		
Document Description	**Start**	**End**
fees.pdf	1	1
pct101.pdf	1	5

Warnings:

Information:

2		72MM-341180-WO-SpecificationAsFiled-2022-10-26.pdf	611444 aaadf87484add17b0c38eb8442230e6bedcf863e	yes	28

Multipart Description/PDF files in .zip description		
Document Description	**Start**	**End**
Specification	1	24
Claims	25	27
Abstract	28	28

Warnings:

Information:

3	Drawings-only black and white line drawings	72MM-341180-WO-FiguresAsFiled-2022-10-26.pdf	111593 aac2bd70123766391bbd8b8faa619a4f12d1029e	no	6
Warnings:					
Information:					
4	Fee Worksheet (SB06)	fee-info.pdf	46147 682e416e1e21df77834348ddb92537a03de3095b	no	2
Warnings:					
Information:					
			Total Files Size (in bytes):	1025414	

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If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PCT (ANNEX - FEE CALCULATION SHEET)

(Original in Electronic Form)

(This sheet is not part of and does not count as a sheet of the international application)

0	**For receiving Office use only**				
0-1	International Application No.				
0-2	Date stamp of the receiving Office				

0-4	**Form PCT/RO/101 (Annex) PCT Fee Calculation Sheet**				
0-4-1	Prepared Using	**ePCT-Filing for data package download Version 4.10.009 MT/FOP 20221019/1.1**			
0-9	**Applicant's or agent's file reference**	**72MM-341180-WO**			
2	**Applicant**	**ARIA PHARMACEUTICALS, INC.**			
12	**Calculation of prescribed fees**	Fee amount/multiplier	Total amounts (USD)		
12-1	Transmittal fee **T**	➪	**130**		
12-2-1	Search fee **S**	➪	**1816**		
12-2-2	International search to be carried out by	**EP**			
12-3	International filing fee (first 30 sheets) **i1**	**1437**			
12-4	Remaining sheets	**9**			
12-5	Additional amount **(X)**	**16**			
12-6	Total additional amount **i2**	**144**			
12-7	i1 + i2 = **i**	**1581**			
12-12	Electronic Filing reduction (Image) **R**	**-216**			
12-13	Total International filing fee (i-R) **I**	➪	**1365**		
12-17	Fee for restoration of priority rights **RP** Number of requests for restoration of priority rights	**0**			
	Total amount of fees for restoration of priority rights				
12-19	**TOTAL FEES PAYABLE (T+S+I+P+RP)**	➪	**3311**		
12-21	**Mode of payment**	**Authorization to charge deposit or current account**			
12-22	**Deposit or current account instructions** The receiving Office	**United States Patent and Trademark Office (USPTO) (RO/US)**			
12-22-1	Authorization to charge the total fees indicated above	✓			
12-22-2	Authorization to charge any deficiency or credit any overpayment in the total fees indicated above	✓			
12-22-3	Authorization to charge the fee for priority document	✓			
12-23	Deposit or current account No.	**504561**			
12-24	Date	**26 October 2022 (26.10.2022)**			
12-25	Name and signature	**Lorna L. Tanner /Lorna L. Tanner/**			